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***Neurogenic Heterotopic Ossification:
Prevalence, Risk Factors, Management and Treatment***

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*“If I have seen farther than others, it is because
I stood on the shoulders of giants.” Isaac Newton*

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Abstract

Introduction: Neurogenic heterotopic ossification (NHO) occurs as a complication of a central nervous system injury and represents the formation of true bone in environments where it is not usually found. It is particularly prevalent among patients with traumatic brain injury (TBI) and traumatic spinal cord injury (TSCI). Once NHO has developed it does not allow for prophylactic drug therapy and surgery, the only effective NHO treatment, carries with it many additional health risks. Thus no “gold standard” exists as regards NHO treatment and new and non-invasive treatment methods are urgently needed to be tested. Extracorporeal shockwave therapy (ESWT) has emerged as one potential treatment method

Objectives of this thesis:

1. To clarify NHO descriptors and clinically significant risk factors associated with NHO in TBI and TSCI patients.
2. To identify the extent of the use of ESWT in the clinical management of NHO in TBI and TSCI patients.
3. To identify the prevalence of NHO in TBI and TSCI patients in specialised and non-specialised units in Australia.
4. To conduct a clinical trial to investigate the effect of ESWT on chronic NHO in patients with TBI.

Methods:

Narrative and systematic reviews with a meta-analysis were undertaken on NHO descriptors and the use of ESWT in the clinical management of NHO. Retrospective audits of TBI and TSCI patients admitted to a tertiary referral hospital and to specialised units were undertaken to determine the prevalence of NHO. A single case study was carried out using the novel intervention of ESWT on a head injured patient with recurrent NHO; this was followed by a larger series of single case research studies using a similar protocol.

Results:

The published literature indicates that sites of NHO following TBI and/or TSCI are usually around the major joints, in particular the hip, knee and elbow. In those patients who do develop NHO, it is an extremely debilitating complication with serious consequences on their functional abilities. From the audit undertaken at the specialised units in Australia the prevalence of NHO in TBI patients and TSCI patients was found to be ~4% and 11%, respectively (Reznik et al., 2014). The audit undertaken at the non-specialised hospital resulted in no records of NHO in TSCI/TBI patients, although six instances of HO (not related to TBI or TSCI) were recorded. (Reznik et al., 2015). The only common risk factors associated with NHO in both TBI and TSCI patients were deep vein thrombosis and/or pulmonary emboli (DVT/PE) (Reznik et al., 2014) with OR of 10.35 and 5.57 for TBI and TSCI, respectively. The remaining risk-factors were found to be discrete to the condition. In particular, spasticity (OR=27.75) followed by a period of intubation >25 days (OR=18.73), urinary tract infection (OR=6.74) and multiple injuries (OR=5.70) were identified as predictors of NHO in TBI patients. Multiple pressure ulcers (OR=5.61) and an AIS impairment score of B (OR= 3.59) were found to be predictors of HO in TSCI patients.

Background data suggest that that ESWT may be associated with clinically significant improvement of range of motion (ROM) in the lower extremity joints of patients with HO, although there is limited evidence in the literature to confirm the effects of ESWT in TBI or TSCI patients. The results of a single case study undertaken in a TBI patient with chronic NHO at the hip were a reduction in pain, an increase in range of motion and improvement in gait parameters, suggesting that ESWT may be a non-invasive, low risk intervention for the management of NHO (Reznik et al, 2013a). Subsequently, a series of single case research studies was undertaken at a specialised rehabilitation hospital on 11 TBI patients with chronic NHO at the hip or knee joint, confirming the results achieved from the single case study. Overall the patients showed a significant reduction in pain and an improvement in all ranges of motion, except internal and external rotation of the hip. Overall function as measured by functional reach (FR) or modified functional reach (MFR) also showed improvement.

Conclusions and clinical implications: The audit conducted at the non-specialised unit, which presented no records of NHO in TBI/TSCI patients, indicated that the

problem may have been related to the coding used for these patients in the hospital. In the audit of the specialised units the prevalence of NHO in TBI patients was found to be less than one third of that found in TSCI patients, with many of the associated risk factors being quite discrete. The results of the series of single case research studies suggest that ESWT may be a non-invasive and effective treatment in the clinical management of NHO following TBI. Further replication of our findings by other groups using our protocol would enhance the evidence for this intervention.

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List of Abbreviations

ACLT	Anterior Cruciate Ligament
AIS	ASIA Impairment Scale
ASIA	American Spinal Injuries Association
ALP	Alkaline Phosphatase
CAD	Coronary Artery Disease
CNS	Central Nervous System
Coop	Dartmouth Coop Functional Health Assessment Charts/Wonca
CPM	Continuous Passive Motion
CR	Computed Radiography
CRPS	Complex Regional Pain Syndrome
CSF	Cerebrospinal Fluid
CSWT	Cardiac Shock Wave Therapy
CT	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine
DR	Digital Radiography
DRG	Dorsal Root Ganglion
DVT	Deep Vein Thrombosis
DXA (DEXA)	Dual-Energy X-ray Absorptiometry
ED	Erectile Dysfunction
EPC (s)	Endothelial Progenitor Cell(s)
EFD	Energy Flux Density
EQ-5D	European Quality of Life 5–Dimensions questionnaire
ESR	Erythrocyte Sedimentation Rate
ESWT	Extracorporeal Shock Wave Therapy
FAM	Functional Assessment Measure
FIM	Functional Independence Measure
FOP	Fibrodysplasia Ossificans Progressive
FR	Functional Reach test
FRS	Faces Rating Scale
GCS	Glasgow Coma Scale
Gy	Gray (<i>the metric (SI) measurement unit of absorbed radiation dose of ionizing radiation</i>)
HBCIS	Hospital-Based Corporate Information System

HBO	Hyperbaric Oxygen Therapy
HLA	Human Leukocyte Antigen
HO	Heterotopic Ossification
HRH	Hampstead Rehabilitation Hospital
IASP	International Association for the Study of Pain
ICC	Intraclass Correlation Coefficient
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification.
IIEF-EF	International Index of Erectile Function – Erectile Function
ISNCSCI	International Standard for Neurological Classification of Spinal Cord Injury
KSS	Knee Society Score
LA	Local Anaesthesia
LDI	Laser Doppler Imaging
LI	Low Intensity
LOS	Length of Stay
MFR	Modified Functional Reach test
MO	Myositis Ossificans
MOP	Myositis Ossificans Progressiva
MR(I)	Magnetic Resonance (Imaging)
NHO	Neurogenic Heterotopic Ossification
NSAID	Non-Steroidal Anti-Inflammatory Drug
NR	Numerical Scale
OA	Osteo-arthritis
OACIS	Open Architecture Clinical Information System
OCEBM	Oxford Centre for Evidence Based Medicine
OLS	Ordinary Least Squares
OR	Odds Ratio
PACS	Picture Archiving and Communication System
PE	Pulmonary Emboli/us
PLIMF	Pulsed Low-Intensity Electromagnetic Field
PNBF	Periarticular New Bone Formation
POA	Para-Osteo-Arthropathy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement
PTA	Post Traumatic Amnesia

PU	Pressure Ulcer
Ras	Reticular activating system
RIS	Radiology Information System
RCT	Randomised Control/led Trial
rESWT	Radial Extracorporeal Shock Wave Therapy
ROM	Range of Motion (Movement)
RT	Radiation Therapy
RTA	Road Traffic Accident
SAP	Serum Alkaline Phosphatase
SIP-68	Sickness Impact Profile-68
SP	Substance P
SPECT	Single-Photon Emission Computed Tomography
SMH	Stoke Mandeville Hospital
SR	Systematic Review
TII	Transition II tools
TBI	Traumatic Brain Injury
THA	Total Hip Arthroplasty
(T)SCI	(Traumatic) Spinal Cord Injury
TTH	The Townsville Hospital
UNSW	The University of New South Wales
URTI	Upper Respiratory Tract Infection
US	Ultrasound
UTI	Urinary Tract Infection
VAS	Visual Analogue Scale
VEGF	Vascular endothelial growth factor
WCC	White Cell Count

Prologue

Forty-four years ago I came across my first spinal injured patient with neurogenic heterotopic ossification (NHO), then known as para-osteo-arthropathy (POA). I was working as a newly qualified physiotherapist at the National Spinal Injuries Centre, Stoke Mandeville Hospital (SMH), Aylesbury, UK and my patient, a young traumatic complete C4/5 tetraplegic, suddenly developed a red, swollen, warm and painful leg. On reporting these signs and symptoms to the registrar I was told to immediately cease all passive movements to the limbs for the next 10 days. Ultrasound did not confirm deep vein thrombosis (DVT), the patient was not put on anti-coagulants but I was not allowed to resume passive movements until the 10 days had passed. On resumption of passive movements, range of movement at the hip was greatly reduced and X-ray later confirmed POA around the hip-joint. The reason for this complication was not confirmed but one of the Senior Registrars, Dr John Silver had presented a paper in 1969 (Silver, 1969) where he noted that one of the most likely causes of POA in the spinal injured patient was micro trauma caused by the passive movements then applied to every joint of every patient, twice daily for the twelve weeks they were immobilised in bed (SMH protocol, 1971; Bromley, 1976). Since every spinal patient received the same physiotherapeutic treatment but not every patient developed POA I decided that this was an assumption that should be investigated.

Four years later in 1975, I was given the opportunity to test this assumption by carrying out audits of four spinal units, two in the UK and two in Israel. A total of 738 spinal patients revealed an incidence of 3.4% of POA, whereas all patients had received passive movements twice daily for the duration of the twelve weeks they were on postural reduction in bed (Goldman, 1980).

Throughout the next 40 years as both a clinician and lecturer in neurological physiotherapy I have sought a non-invasive management/ treatment for this debilitating complication of neurological injuries, now termed NHO. The studies reported in this thesis have allowed me to further investigate NHO and its prevalence, risk factors and management and to rigorously explore a possible new, non-invasive treatment for this debilitating complication of neurological injuries. For this I am grateful.

Chapter 1. Introduction

1.1 Thesis background

Heterotopic ossification (HO) is defined as the formation of lamellar bone inside soft-tissue structures where bone does not normally exist (Bossche & Vanderstraeten, 2005; McCarthy & Sundaram, 2005; Simonsen, Sonne-Holm, Krashennikoff, & Engberg, 2007). It may be acquired following trauma, surgery (e.g. hip arthroplasty), burns, fractures, dislocations, soft-tissue trauma, or neurologic damage (van Kampen, Martina, Vos, Hoedemaekers & Hendricks, 2011). The term heterotopic ossification (HO) refers only to the environment in which the bone process occurs and not to the type of bone formed. HO is a result of true osteoblastic activity and is not the result of tissue transformation (Mavrogenis, Soucacos, & Papagelopoulos, 2011).

HO was first described in children with myositis ossificans progressiva by Patin in 1692. This description was further clarified by Reidal in 1883 (Bossche & Vanderstraeten, 2005) and in 1919 the first modern report of HO was published by Déjerine & Ceillier based on their observations of the acquired ossification around the medial femoral condyle in a group of World War I veterans who had become paraplegic from intramedullary gunshot wounds. At that time the relationship between oedema and traumatic lesions of the nervous system was already established. Several terms, based upon hypothetical causative and developmental mechanisms, have been used to denote this condition including para-osteo-arthropathy (POA), myositis ossificans (MO), periarticular new bone formation (PNBF), periarticular ectopic ossification, neurogenic osteoma, neurogenic ossifying fibromyopathy, and heterotopic calcification (Balboni, Gobezie, & Mamon 2006; Mendelson, Grosswasser, & Najenson 1975). HO is the name used almost exclusively in today's literature (Genêt et al., 2011; Mavrogenis et al., 2011; Sakellariou, Grigoriou, Mavrogenis, Soucacos, & Papagelopoulos, 2012).

Extracorporeal shock wave therapy (ESWT) is a non-invasive method of therapy which uses externally generated high-intensity shock waves to improve chronic, painful conditions of the musculoskeletal system. Several studies have suggested that ESWT could be used in the treatment of heterotopic ossification (HO)-associated complications associated with a number of conditions including traumatic brain injury (TBI), spinal cord injury (SCI), total hip arthroplasty (THA), and burns (Brissot et al., 2005; Buselli et al., 2010; Reznik et al., 2013a; Torrance and deGraauw, 2011).

Physiotherapists, and in particular those dealing with patients with neurological insults, are aware of one particular type of HO, neurogenic heterotopic ossification (NHO) occurring in patients with neurological conditions and the impact that such a complication can have on a group of already severely functionally compromised individuals.

1.2 Aims

The aims of this thesis were:

1. To investigate the prevalence of NHO in specialised and non- specialised units
2. To identify the risk factors associated with NHO
3. To determine the current management protocol and to investigate the therapeutic potential of extracorporeal shock wave therapy (ESWT) for clinical management of NHO in patients with TBI

1.3 Objectives

The objectives of this thesis were:

1. To review the published literature on NHO descriptors
2. To review the published literature on ESWT
3. To conduct a systematic review of the published literature for the evidence of ESWT as a treatment for NHO
4. To conduct an audit to establish the prevalence of NHO in TBI and TSCI patients in specialised and non-specialised units in Australia
5. To conduct a series of single case studies to investigate the effects of ESWT on NHO in patients with TBI

1.4 Guiding questions

For the first part of this thesis there were a number of guiding questions:

1. What is the evidence for the effectiveness of ESWT in the treatment of NHO in TBI and TSCI patients?
2. What is the prevalence of NHO in TBI and TSCI patients in specialised units?
3. What is the prevalence of NHO in TBI and TSCI patients in non-specialised units?
4. How effective is ESWT in the treatment of NHO in TBI patients?

1.5 Rationale for the thesis

As a result of the discrepancies in the prevalence of NHO in both TBI and TSCI patients (as discussed in Chapter 2), there is an urgent need to establish the extent of this clinical problem. Since routine screening is not in place in the majority of specialised units or tertiary hospitals, clinical diagnosis at this stage does not allow for prophylactic drug therapy and since the surgical option carries with it many additional health risks (Melamed et al., 2002), it is imperative to find a better solution. No “gold standard” exists as regards treatment protocols and many ambiguous findings concerning the clinical outcomes of NHO treatment still remain unchallenged (Aubut, Mehta, Cullen, & Teasell, 2011; van Kampen et al., 2011).

A retrospective study carried out almost 40 years ago (Goldman, 1980), suggested as a potential risk factor, the time taken following trauma until admittance to a specialised unit. By auditing both a tertiary facility and a specialised unit in Australia, this proposal was challenged in this study. In addition to the clinical audits, a preliminary literature review indicated positive results on the therapeutic use of ESWT on soft tissue injuries. A further comprehensive narrative literature review was carried out to address the prevalence, risk, pathophysiology and treatment options for NHO to date and a systematic literature review was conducted on the effectiveness of ESWT for NHO.

The positive results from the case report on clinical application of ESWT to treat NHO were used as a basis for a small clinical trial, the results of which need to be substantiated by larger studies.

1.6 Hypotheses for clinical trial

H1: Treatment of chronic NHO around the hip/knee joint in TBI patients using four applications of ESWT will lead to:

- Reduction of pain – as measured by the Visual Analogue Scale (VAS) in the form of the Faces Rating Scale (FRS)
- Increase in function by demonstrating:
 - Increase of range of movement in hip/knee joints
 - Increase in the Functional Reach Test (FRT) /Modified Functional Reach Test (MFRT)
 - Improved spatio-temporal measures of gait as measured by the 10 metre walk and the 6 minute walk tests in those patients who are ambulant
 - Increase in the Functional Independence Measure (FIM) score
 - Increased score in the European Quality of Life 5- Dimensions questionnaire (EQ-5D)

H2: Treatment of chronic NHO around the hip/knee joint in TBI patients using four applications of ESWT will demonstrate a positive physiological effect on NHO i.e. a reduction in the size of NHO as measured by plain X-ray.

1.7 Schematic overview

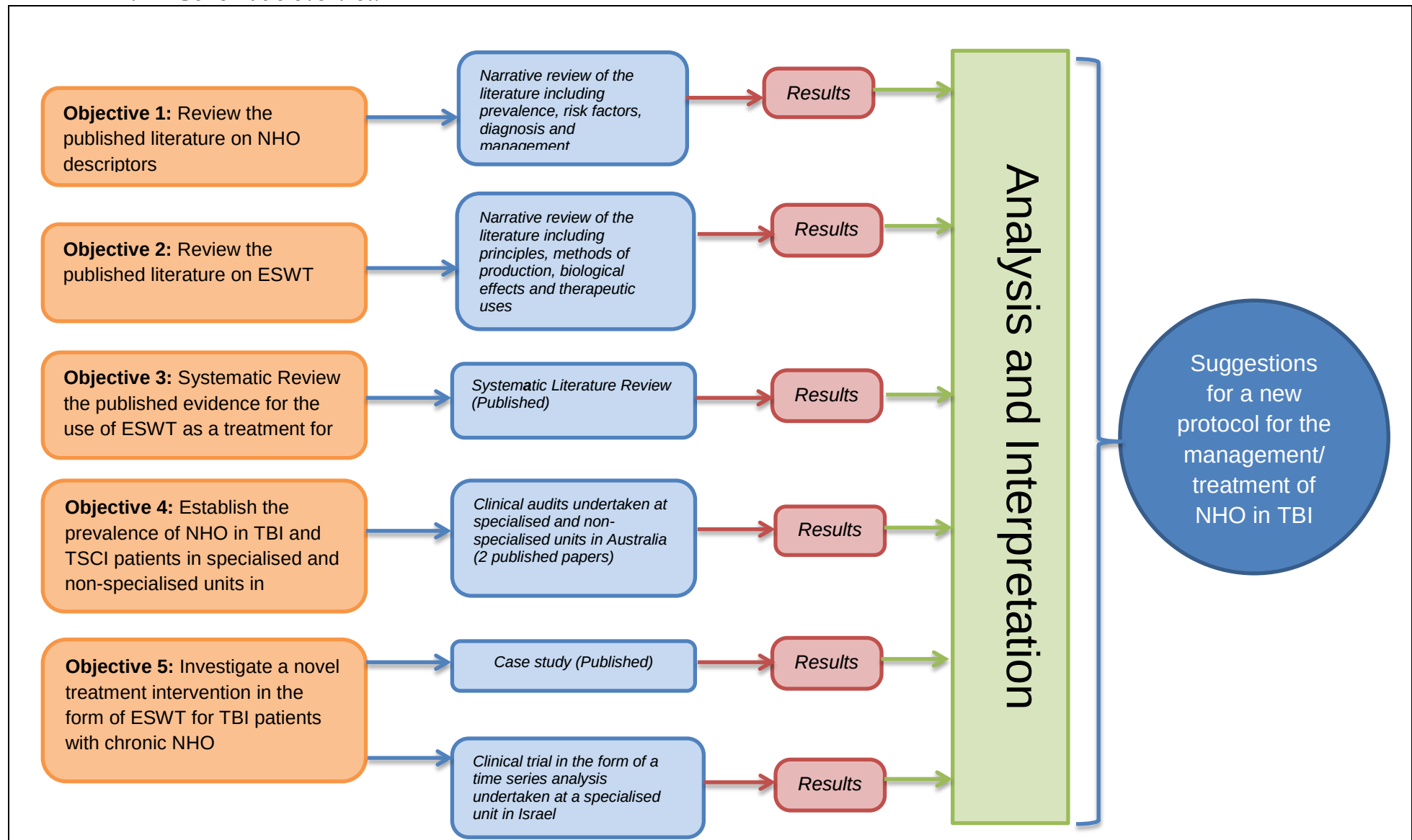


Figure 1.1 Neurogenic Heterotopic Ossification: Prevalence, Risk Factors, Management and Treatment.

1.8 Methodologies of thesis

1.8.1 Narrative literature review

Chapter 2, a review of the published literature on NHO descriptors and Chapter 3, a review of the published literature on ESWT, are narrative literature reviews. The narrative literature reviews, also known as *narrative overviews* or *unsystematic narrative reviews* are comprehensive syntheses of previously published information (Green, Johnson, & Adams 2006). Narrative overviews are extremely useful when reviewing large bodies of knowledge as was the case for both the NHO descriptors and the published literature on ESWT. Baumeister (2013) suggested that narrative reviews were valuable if the goal of the review, as in this case, was to formulate a new theory linking together diverse strands of work. In this thesis the narrative literature reviews on NHO and ESWT will be linked in subsequent chapters in order to put forward a possible new treatment strategy for the treatment of NHO (Prinstein and Matterson, Part III, Chapter 8, 2012).

1.8.2 Systematic literature review

Chapter 4 is a systematic review (SR) with a meta-analysis of the published data available on the use of ESWT as a treatment for heterotopic ossification (HO). This review was devised according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009). The systematic review was carried out as described in Chapter 4 and this paper was published in Physical Therapy Reviews in 2013 (Reznik et al., 2013b).

1.8.3 Clinical audits

The clinical audit was first introduced into clinical research by Florence Nightingale during the Crimea War (1853-1855). Health services are now using audits as an integral part of their quality-improvement strategies and accreditation processes (UNSW, 2009).

Definition of a clinical audit:

The purpose of clinical audits is to systematically review the quality and outcomes of care against predetermined criteria, with the aim of identifying areas for improvement and then developing, implementing and evaluating

strategies intended to achieve that improvement. (Travaglia, & Debono, 2009).

In order to establish the prevalence of NHO in TBI and TSCI patients in specialised and non-specialised units in Australia two separate audits were conducted for this thesis. Both studies were based on retrospective data. In The Townsville Hospital (TTH), the tertiary non-specialised TBI/TSCI health-care facility, the data were collected between July 2007 and December 2012; in the specialised TBI/TSCI units at the Hampstead Rehabilitation Hospital (HRH), the data were collected between January 2007 and December 2012. Two distinct information systems identified the patients; the Hospital-Based Corporate Information System (HBCIS) and Transition II (TII) tools were the identification systems employed at TTH and the Open Architecture Clinical Information System (OACIS) was used at the HRH. Almost 1900 and 500 TSCI/TBI patients were identified from TTH and HRH, respectively.

The outcomes of these audits are detailed in Chapters 5 and 6. The findings were published in the Health Care Manager (2015) (Reznik et al., 2015) and the Journal of Musculoskeletal Neuronal Interactions (2014) respectively (Reznik et al., 2014).

1.8.4 Case study

As defined by Portney and Watkins (2008) “*a case study is an intensive investigation designed to analyse and understand those factors important to the aetiology, care and outcome of the subject’s problems*”.

Neurogenic heterotopic ossification (NHO) is a unique condition occurring in a relatively distinct group of patients. ESWT has been used as a treatment procedure in a number of musculoskeletal conditions (see Chapter 3) but rarely in the case of NHO on a TBI patient.

In order to develop a clinical knowledge-base in this area which had such a paucity of published literature, a case study using ESWT as a treatment for chronic NHO in a TBI patient was undertaken. The methodology of this study and the results were published in Brain Injury (2013) and are detailed in Chapter 7.

1.8.5 Series of clinical single case research studies

For the reasons outlined below the traditional randomised controlled trial, which requires a large homogenous population with a similarly large control group, is not feasible as a study design to demonstrate the effectiveness of ESWT as a treatment for NHO. A more pertinent strategy in which to study such effects is the single subject research design allowing conclusions to be drawn about a treatment based on the responses of an individual patient under controlled conditions.

The international NHO statistics in the TBI population indicate that it is a relatively rare condition (~4%) occurring in a very specific patient group. The global incidence rate of TBI is estimated at 200 per 100 000 people per year; however, this rate is uncertain due to variations in definition and methods of data collection (Bryan-Hancock and Harrison, 2010).

Following the encouraging results of the published case report by Reznik et al., (2013a), a series of single case research studies was designed. Since there were no published data on TBI patients specifically (all previous publications involved a wide heterogeneity of conditions) all patients recruited to this series of single case studies were traumatic brain injured patients and the joints involved were limited to the hip or knee.

The results obtained from these studies were analysed using the Tau-U method. Tau-U is a method for measuring data non-overlap between two phases such as baseline and treatment. It is a “distribution free” nonparametric technique, with statistical power of 91% to 95% of ordinary least squares (OLS) linear regression when data conform to parametric assumptions (Parker, Vannest, Davis, & Sauber 2010).

The details of these studies are reported in Chapter 8.

Chapter 2. Heterotopic Ossification (HO)

2.1 Introduction

Under pathological conditions in post-natal life, bone occasionally forms in tissues other than those comprising the skeleton. Such bone forms as the result of heteroplasia, a replacement of normal soft tissue of the body by abnormal heteroplastic or heterotopic bone (Goldman, 1980). The term heterotopic ossification (HO) refers only to the environment in which the bone process occurs and not to the type of bone formed. HO is a result of true osteoblastic activity and is not the result of tissue transformation (Mavrogenis et al., 2011).

HO was first identified in 1883 by Reidel, a German physician. First described as “para-osteo-arthritis” by French neurologists Dejerne and Ceillier in 1918, based on observations of patients with traumatic paraplegia in World War I (Déjerne & Ceillier, 1919), HO has been given multiple names including para-osteo-arthritis, myositis ossificans, periarticular new bone formation, periarticular ectopic ossification, neurogenic osteoma, neurogenic ossifying fibromyopathy, and heterotopic calcification (Balboni et al., 2006; Mendelson et al., 1975). As stated in Chapter 1, HO is the name used almost exclusively in today’s literature (Genêt et al., 2011; Mavrogenis et al., 2011; Sakellariou et al., 2012).

2.1.1 Classification

HO has been classified into the post-traumatic (also known as myositis ossificans circumscripta), neurogenic, and myositis ossificans progressiva (MOP) or fibrodysplasia ossificans progressiva (FOP) types (Balboni et al., 2006; Genêt et al., 2012; Mavrogenis et al., 2011). Post-traumatic HO typically follows injuries such as fractures and dislocations, muscular injuries and operative procedures, such as joint arthroplasty and may also include the HO following severe burns (Garland, 1991; Kocic, Lazovic, Mitkovic, & Djokic 2010; Mavrogenis et al., 2011; Siemers, Stollwerck, Lohmeyer, Namdar, & Mailander, 2010). Neurogenic heterotopic ossification (NHO) mainly occurs following spinal trauma and head injuries (Cipriano, Pill, & Keenan, 2009; Teasell et al., 2010). Additional neurological disorders associated with the development of NHO include stroke, viral and bacterial infections such as encephalitis, poliomyelitis, tetanus, tabes dorsalis, syringomyelia, and other conditions

such as anoxic encephalopathy, Guillain-Barré syndrome, and prolonged pharmacologic paralysis during mechanical ventilation (Mavrogenis et al., 2011; Mendelson et al., 1975; Zeilig et al., 2006). The MOP and FOP types represent two genetic syndromes characterized by HO (Cohen et al., 1993; Shore & Kaplan, 2010, Shore et al., 2002; Smith, Russell, & Woods, 1976).

The Brooker Classification for HO of the hip (Brooker, Bowerman, Robinson, & Riley, 1973) is the most commonly used classification in the literature (Mavrogenis et al., 2012). It is based on anteroposterior radiographs of the hip and is therefore a relatively simple and valid measurement that appears to correlate well with the clinical picture of hip function (Figures 2.1, 2.2).

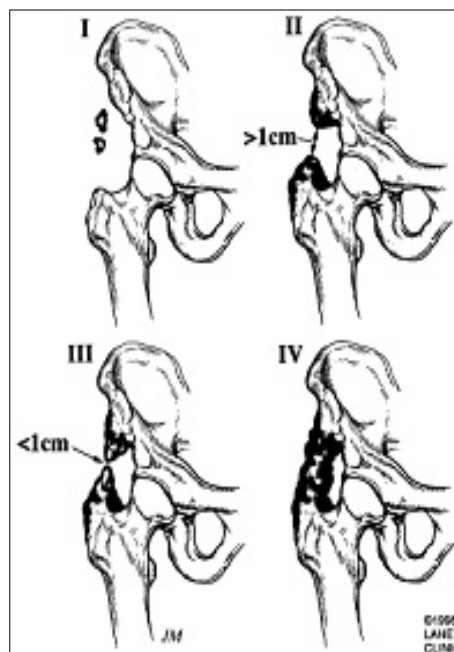


Figure 2.1 HO progression of the hip (Brooker's Classification).

Grade I	Ossification islands around the hip
Grade II	Bone projection of pelvis or proximal femur with at least 1 cm away from the opposite surface
Grade III	Bone projection of pelvis or proximal femur reducing space between opposite surface lower than 1 cm
Grade IV	Hip ankylosis

Figure 2.2 Brooker's Classification of Heterotopic Ossification around the hip (Brooker et al., 1973).

Brooker's classification was, however, found to be misleading when applied to NHO (Mavrogenis, Guerra, Staals, Bianchi, & Ruggieri, 2012). Mavrogenis and colleagues (2012) proposed a new classification based upon (1) the anatomical localization of the HO as shown on axial computed tomography (CT) scans of the hip and proximal femur; (2) clinical ankyloses of the hip-joint, and (3) the aetiology of the neurological injury (TBI/TSCI).

2.1.2 Localisation

Sites for the deposition of HO appear to be dependent upon the underlying aetiology. The most common sites of traumatic HO, or myositis ossificans circumscripta, as it is termed when it forms within the muscle include pectoralis major, biceps, brachialis and biceps, quadriceps (Wang, Lomasney, Demos, & Hopkinson, 1999), and more rarely, the feet (Allard, Thomas, & Nicholas Jr, 1997). Other less common sites include abdominal incisions (Koolen, Schreinemacher, & Peppelenbosch, 2010), abdominal wounds (Reardon, Tillou, Mody, & Reardon, 1997), the kidneys (Gohji et al., 1987), the uterus (Sethi, Bhatnagar, & Sethi, 2008), the cavernous body of the penis (corpora cavernosa) (Eisenberg, Smith, Shindel, & Lue 2011), and the gastrointestinal tract (Haque, Eisen, & West, 1996). The most common postsurgical site of HO is the hip following hip arthroplasty (Pakos et al., 2009). In spinal cord injury, HO is always found below the level of the lesion (Dejerine & Ceillier, 1919; Teasell et al., 2010) and is usually located around the major joints, the hip being the most common site of occurrence following traumatic spinal cord and traumatic brain injury (Cipriano et al., 2009; Simonsen et al., 2007) (Figure 2.3). In the genetically-associated forms of HO (the MOP and FOP syndromes) the distribution is more extensive often leading to widespread ankyloses (Shore et al., 2010) (Plate 2.1).

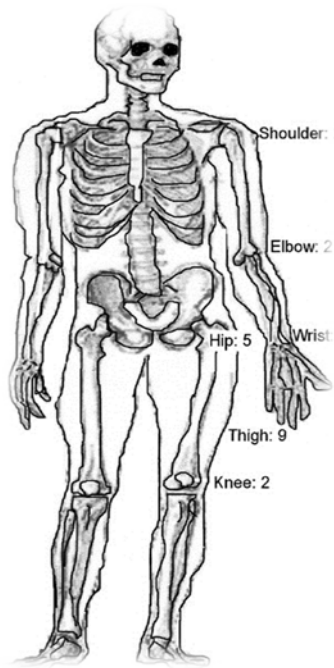


Figure 2.3

Figure 2.3 Schematic skeletal diagram indicating major joints where NHO occurs. (Simonsen et al., 2007).



Plate 2.1

Plate 2.1 Clinical Features of FOP showing widespread HO (Shore et al., 2010)

2.2 Neurogenic heterotopic ossification (NHO)

In view of the diverse aetiologies associated with the development of HO and the various possible pathophysiological mechanisms concomitant with each, this chapter will focus on neurogenic heterotopic ossification (NHO) and in particular NHO which occurs following traumatic brain injury (TBI) and traumatic spinal cord injury (TSCI). (Plate 2.2)

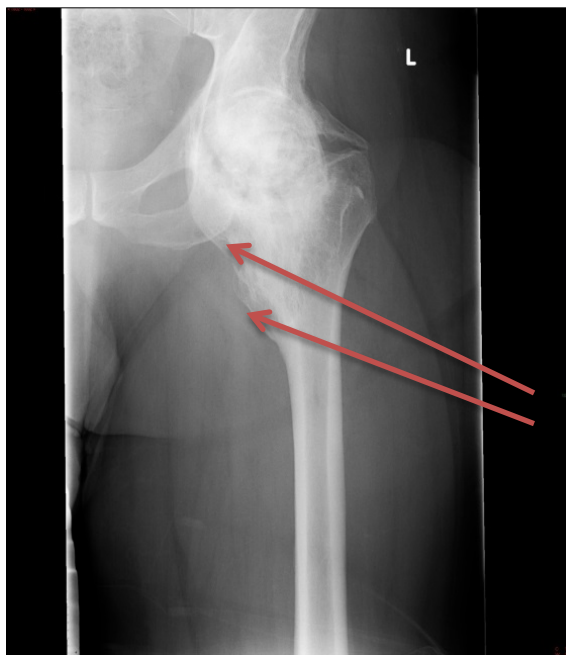


Plate 2.2 Arrows show NHO around the hip of a TBI patient. (Reznik et al., 2013a)

2.2.1 Prevalence

The prevalence of clinically significant NHO in TBI patients has been estimated as being between 10% and 23% (Bossche & Vanderstraeten, 2005; Cipriano et al., 2009; Sakellariou et al., 2012). In TSCI patients the prevalence of NHO has been reported as being between 10% and 53% (Sakellariou et al., 2012; Teasell et al., 2010). Both these figures show a substantial increase from the earlier estimates of 3% and 3.6% described by Damanski (1961) and Goldman (1980) for TBI and TSCI, respectively. These high discrepancies in the prevalence of NHO would appear to be due to the fact that the majority of centres confirm the presence of NHO only if and when it becomes clinically significant i.e. causes pain, interferes with movement and/or restricts function. These inconsistencies are further highlighted in a study by Citak and colleagues who described the incidence of NHO at their level-1 trauma centre as being 21.9% in the traumatic SCI patients (Citak et al., 2012). In this study, however, all TSCI patients were routinely screened for NHO every two weeks by experienced radiologists.

Seipal and colleagues conducted a four year retrospective analysis of 1,463 patients treated at a clinic for early neurological rehabilitation (Seipal et al., 2012). The overall prevalence of NHO reported by the authors was ~2%, much lower than that recorded by any of the previous work. It is important to note, however, that almost one quarter of

their participants included patients suffering from non-traumatic neurological disorders (Seipal et al., 2012). These results concur with those of Damanski (1961) who described the incidence of NHO to be lower in patients suffering from non-traumatic neurological disorders (Damanski, 1961). Interestingly, the prevalence of NHO after TSCI is lower in paediatric patients than in adults, and spontaneous resorption of NHO has been reported exclusively in children (Hitzig et al., 2008).

2.2.2 Possible causative factors

McCarthy & Sundaram (2009) suggested that four factors are necessary for the initiation and progression of NHO: (i) trauma, (ii) a signal from the site of injury, possibly a bio-active molecule secreted from the injured tissue, (iii) a supply of non-specific mesenchymal cells, and (iv) an appropriate environment conducive to the continued production of heterotopic ossification. Other factors which have been suggested as possible contributors to the formation of NHO include micro-traumatic lesions, immobilization, infection, pressure ulcers and vasomotor disturbances (Catz et al., 1992; Snoecx, De Muynck, & Van Laere, 1995). Passive manipulation of joints has been suggested to have potential causative effects (Daud, Sett, Burr, & Silver, 1993; Silver, 1969) with the implication that forcible ranging of joints can cause microtrauma and haemorrhages, leading to NHO formation (Botte et al., 1997; Damanski, 1961). Other studies have, however, shown favourable effects of active and passive exercising of joints within the pain-free range (Goldman, 1980; Linan, O'Dell, & Pierce, 2001; van Kuijk, Geurts, & van Kuppevelt, 2002).

The exact underlying cause of NHO formation following trauma in the central nervous system (CNS) is unknown, although the role of genetic factors such as human leukocyte antigen (HLA) system has been suggested (Chauveau et al., 2004; Larsen et al., 1981). This hypothesis was based on the fact that some HLA alleles are strongly associated with chronic inflammatory pathologies of the axial skeleton, such as ankylosing spondylitis (Weiss et al., 1979). Weiss and colleagues (1979), however, failed to detect any association between HLA and NHO in their study that compared distribution of HLA alleles between well-phenotyped NHO patients and ethnically matched non-NHO controls.

Chauveau and colleagues (2004) suggested that significant differences exist in gene expression profiles of HO and normal bone tissues. In particular, the authors found a number of genes involved in bone-formation processes, including osteocalcin (*BGLAP*), osteonectin (*SPARC*) and type 1 collagen (*COL1A1*), to be upregulated in HO (Chauveau et al., 2004). In a later study, Chauveau and colleagues (2008) hypothesised that heterotopic osteogenesis following head injury may be mediated by the CNS, suggesting that humoral factors may be altered in the circulation of these patients. Indeed, the authors found decreased serum levels of leptin associated with decreased adrenergic signalling in HO biopsies of TBI patients, though the specific β -receptor subtype(s) associated with leptin remained unclear (Chauveau et al., 2008). The authors suggested that hypothalamic leptin signalling contributes to HO formation after brain injury. This is in line with previous findings suggesting that leptin has direct effects on proliferation, differentiation, and mineralization of human cultured osteoblasts (Reseland et al., 2001). Furthermore, circulating alkaline phosphatase (ALP), a protein associated with active bone formation, dramatically increased during the first week in patients who developed heterotopic ossification post-neurological injury. Normalisation of its serum levels did not, however, correlate with maturation of ectopic bone (van Kujik et al., 2002).

2.2.3 Risk factors

Many risk factors for NHO in the TBI and TSCI patients have been recognised (Table 2.1 and Table 2.2); however, their biological basis is often unclear. These risk factors include vascular stasis, oedema, and prolonged swelling as possibly contributing to NHO formation (Beilby & Mulligan, 2008; Bradleigh et al., 1992). Demographic factors such as age, gender and ethnicity have also been suggested to increase the risk of NHO (van Kujik et al., 2002). Some clinical characteristics and factors associated with the clinical management of traumatic neurological injuries such as length of time in coma, and artificial ventilation in patients with TBI (van Kampen et al., 2011), as well as completeness and level of spinal cord injuries in TSCI patients (Coehlo & Beraldo, 2009; Goldman, 1980), have been suggested to be associated with the risk of developing NHO. Marked spasticity, length of time before being admitted to a specialised unit, associated fractures at the time of injury, pressure ulcers and urinary

tract infections have also been suggested as possible risk factors in the development of NHO in TSCI patients (Citak et al., 2012; Goldman, 1980).

Table 2.1

Risk factors for developing neurogenic heterotopic ossification following traumatic spinal cord injury.

Risk Factors In Development Of NHO In Traumatic Spinal Cord Injuries		
Risk Factors	Goldman, 1980	Coelho & Beraldo, 2009
Gender	M	M
Age	20-40	Not documented
Level of Injury	Thoracic lesion	Thoracic lesion
Complete/Incomplete	Complete	Complete
Spasticity	Absent/Mild	Absent/Mild
Pressure Ulcers	Present	Present
DVT	No	No
Length of Stay	>6 weeks	Not documented
Type of injury	RTA	Not documented
Smoking	Not documented	No
Urinary complications	Not documented	Present
M=Male; F= Female; DVT=Deep Vein Thrombosis; RTA= Road Traffic Accident		

Table 2.2

Risk factors for developing neurogenic heterotopic ossification following traumatic brain injury.

Risk Factors in Development of NHO in Traumatic Brain Injuries		
Risk factors	Simonsen, 2007	van Kampen, 2011
Gender	M =F	M >F
Age	Median 23 years	Median 35 years
Spasticity	Severe	Absent/mild
Length of Stay	Median 192 days	Not documented
Immobilisation	Yes	Not significant
SAP levels	Raised	Not documented
Mechanical ventilation	Not documented	Mean 16.50 days
Autonomic dysregulation	Not documented	Significant
Long bone fractures	Not documented	Not significant

M=Male; F= Female; SAP= Serum Alkaline Phosphate

Although demographic factors such as male sex and young age (20-30 years) have been suggested as risk factors (Goldman, 1980; Wittenberg, Peschke, & Botel, 1992), this remains controversial. The most definitive risk factors in TBI patients would appear to be spasticity, a period of intubation greater than 25 days, urinary tract infections and multiple injuries. In a prospective study of 97 severe head trauma patients with Glasgow Coma Scale (GCS) score <8, van Kampen et al., (2011) described 13 patients (13%) who developed clinically significant NHO. Univariate analysis of this group of patients revealed that prolonged coma duration and mechanical ventilation, coexistent surgically treated bone fractures and clinical signs of autonomic dysregulation were potential risk factors for developing clinically relevant NHO.

2.2.4 Possible pathophysiological mechanisms

The pathophysiological mechanisms associated with NHO formation seems to be more complex than simply inappropriate differentiation of fibroblasts into bone-forming cells, as originally thought (Sakellariou et al., 2012). The ectopic bone formation may include osteoprogenitor stem cells lying dormant within soft tissues. With a proper stimulus, the stem cells differentiate into osteoblasts and begin osteoid formation, an un-mineralized, organic portion of the bone matrix that forms prior to the maturation of

bone tissue, eventually leading to mature heterotopic bone showing cancellous bone and mature lamellar bone, vessels, and bone marrow within the formation (Mavrogenis et al., 2011; Sawyer, Myers, Rosier, & Puzas, 1992). The appropriate stimuli that can activate the osteoprogenitor stem cells may include bio-available calcium in adjacent skeleton, soft tissue oedema, vascular stasis, tissue hypoxia, and mesenchymal cells with osteoblastic activity (Mavrogenis et al., 2011).

It has been observed that unconscious patients with multiple injuries produce more abundant bony callus than conscious patients with similar fractures. Accordingly, it has been shown that unconscious patients have accelerated healing of fractures (De Bastiani et al., 1992; Perkins and Skirving, 1987; Spencer, 1987). Bidner and colleagues (1990) conducted a study on osteoblasts isolated from 19 day old Sprague-Dawley rats treated with the sera of hospitalised patients. The sera were obtained from patients who had a head injury and lower limb fractures; those who had a head injury with no fractures; those who had lower limb fractures and no head injury; and a control group without any injury or neural or osseous disorder. The results indicated that mitogenic activity of the rat osteoblasts was increased in the serum from patients who had only a head injury or head injury and fractures as compared with the serum of patients who had only lower limb fractures or controls (Bidner, Rubins, Desjardins, Zukor, & Goltzman, 1990). (Figure 2.4).

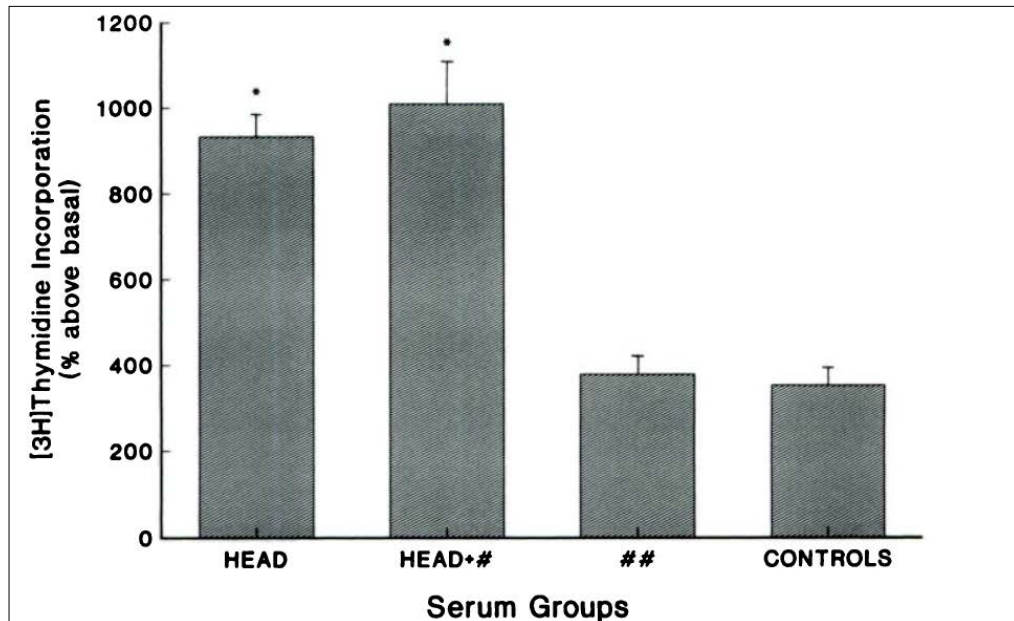


Figure 2.4 Mitogenic activity on osteoblastic cells of serum from patients who had only a head injury (HEAD); those who had a head injury and fractures (HEAD +##); those who had fractures only (##); and control subjects (Bidner et al., 1990).

Recent studies further substantiated these findings and more importantly, suggested that the extent of bone healing and callus formation is independent of the severity of the brain injury (T-Y. Yang, Wang, Tsai, & Huang, 2012).

Further evidence of this has been provided by Gautschi et al., (2009) in his investigation of the osteoinductive potential of human cerebrospinal fluid (CSF). The authors demonstrated (*in vitro*) increased proliferation of osteoblasts treated with the CSF of patients with TBI as compared to osteoblasts treated with CSF of non-TBI patients or controls (Figure 2.5).

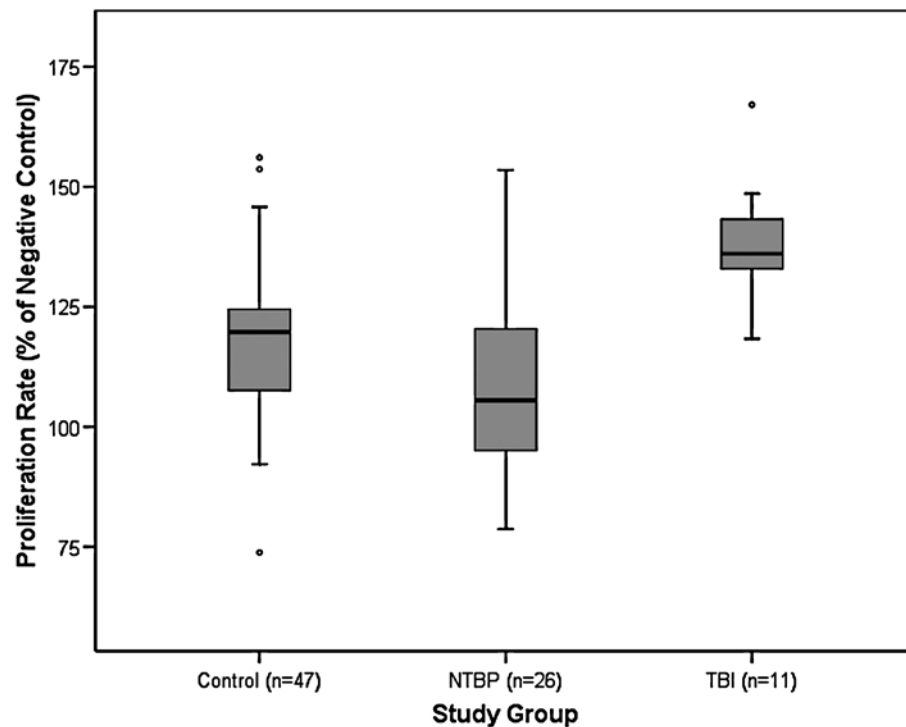


Figure 2.5 Boxplot showing the osteoblastic proliferation rate in three patient subgroups.

The x axis indicates the three different groups (control, non-traumatic brain pathology [NTBP], and traumatic brain injury [TBI]), and the y axis indicates the proliferation rate (as a percentage of the negative internal plate control). The circles represent the outlying values and the bold lines inside the boxes are the medians. (Gautschi et al., 2007).

Collectively these results suggest a pro-osteogenic secretion into the circulation possibly regulated by the brain (Bidner et al., 1990). It is known that the secreted cytokine profile dramatically changes after TBI or TSCI. Among these cytokines, semaphorin 3A (SEMA3A), an axonal guidance molecule, has been shown to be upregulated in response to TSCI (De Winter et al., 2002) and importantly, has vital implications in the formation of the skeletal system. In particular, SEMA3A has been shown to have a dual role in bone homeostasis as it is able to suppress osteoclastic bone resorption and to increase osteoblastic bone formation (Hayashi et al., 2012). This makes SEMA3A a recognised therapeutic target for NHO, the potential of which needs to be thoroughly investigated in other contexts, i.e. animal models for acquired heterotopic ossification.

The ectopic bone developed in post-TBI patients is histologically and radiologically similar to normal mature bone and can be distinguished from a simple calcification by its osteoblastic capacity (Cipriano et al., 2009; van Kampen et al., 2011). Typically,

lower levels of osteocalcin, a pro-osteoblastic non-collagenous protein, induce osteoblast proliferation in the early proliferation stage, while higher osteocalcin levels prevent excessive mineralization (Chauveau et al., 2004).

In the spinal cord injured patient NHO originates from the connective tissue lying between the muscles, outside of the joint capsule, and the joint space and capsule are preserved (van Kuijk et al., 2002; Yildiz & Ardiç, 2010). NHO may be contiguous with the bones, but does not involve the periosteum. Muscle fibrils are not usually involved, but they may be compressed by calcified soft tissue and local muscle necrosis may develop (Yildiz & Ardiç, 2010). A widely accepted theory suggests that NHO begins as an oedematous, inflammatory reaction with an increased blood flow in the affected soft tissue area. First, exudative cell infiltration takes place; then, fibroblastic cell proliferation occurs, followed by osteoid formation and finally, bone matrix development (Rossier et al., 1973). Within the first two weeks, primitive bone foci are observed as small masses in the fibroblastic mesenchymal reaction area, primarily in the periphery. Osteoblasts produce tropocollagen, which is a polymerized form of collagen, and synthesize alkaline phosphatase (ALP) (Bolger, 1975). ALP degrades pyrophosphate, which is a compound that prevents calcium deposition. The newly developing ectopic bone matrix inactivates nearby pyrophosphate. Therefore, ALP allows precipitation of calcium and mineralization of bone matrix (Pape, Marsh, Morley, Krettek, & Giannoudis, 2004; van Kuijk et al., 2002; Yildiz & Ardiç, 2010). (Figure 2.6).

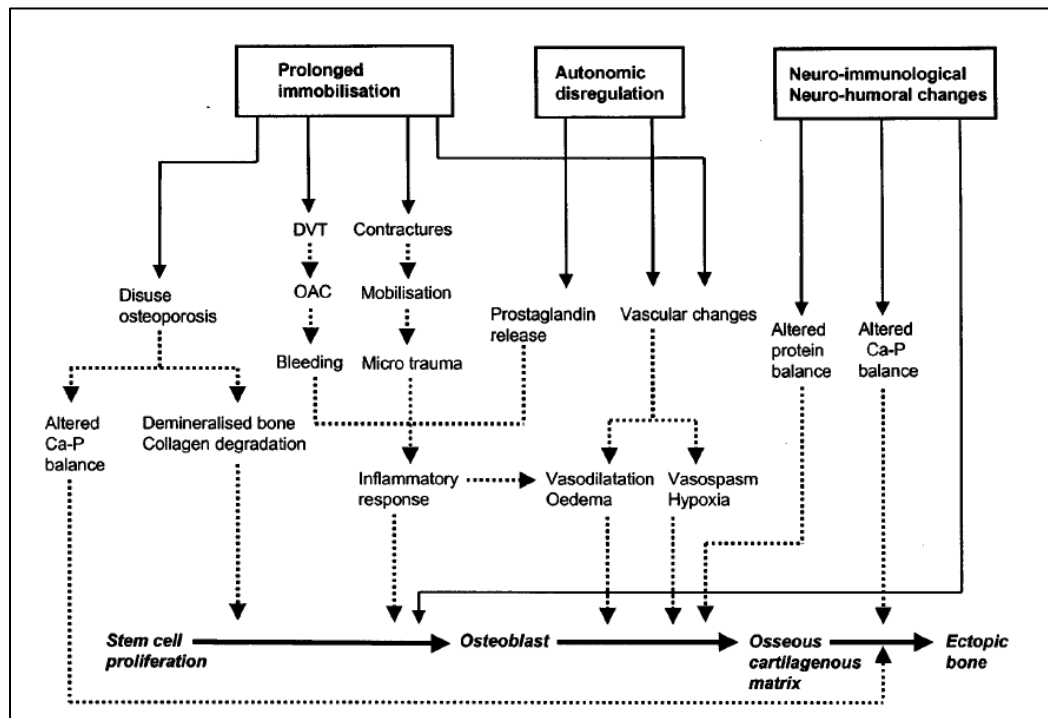


Figure 2.6 Suggested pathophysiologic mechanisms of NHO in SCI patients.

DVT: deep venous thrombosis; OAC: oral anti-coagulant (van Kuijk et al., 2002).

2.2.5 Clinical diagnosis

Diagnosis of early NHO is based predominantly on clinical signs and symptoms. These early symptoms, which include pain, fever, swelling, erythema, and decreased joint motion, are typically seen in early NHO but may also be easily confused with deep venous thrombosis (DVT), infection, and trauma (Shehab, Elgazzar & Collier, 2002). The time of presentation is usually two months post neurological injury but can range from two weeks to twelve months post injury (Van Kuijk et al., 2002).

2.2.5.1 Laboratory investigations

Serum alkaline phosphatase (SAP) levels have been reported to parallel the activity of ossification (Furman, et al., 1970). SAP levels start to rise about seven weeks before the first clinical signs of NHO become apparent, exceed normal levels one week later and reach peak levels three weeks after the first clinical signs (Orzel & Rudd, 1985). Subsequently the SAP levels gradually decline to normal. The normative value for alkaline phosphatase (ALP) is 53 - 128 units per litre (U/L) in a 20 to 50 year-old man and 42 -98 U/L in a 20 to 50 year-old woman. Adults over 61 years have normative values of ALP of 51-153 U/L (Burtis, Ashwood & Bruns, 2012; Collins, 2008).

Elevated erythrocyte sedimentation rates (ESR) have also been reported to reflect the initial “inflammatory” phase of NHO, but both SAP and ESR rates have not been proved to be NHO-specific (van Kuijk et al., 2002). Similarly, the urinary concentration of hydroxyproline, another collagen metabolite, was found to parallel the level of SAP in TSCI patients with NHO (Chantraine, Nussgens & Lapiere 1995), however, this may also occur in patients with urinary tract infection (UTI) or upper respiratory tract infection (URTI) (van Kuijk et al., 2002).

2.2.5.2 Imaging

2.2.5.2.1 Three phase bone scan

In the early stages of NHO the bone formation consists primarily of osteoid, which shows a high uptake of bone-targeting (osteotropic) radionuclides through which it is readily detectable by 99m Technetium bone scanning. The three phase bone scan is able to detect NHO as early as two and a half weeks after TSCI (Freed, 1982). These bone scans return to normal as the NHO matures, usually within 6-18 months after the initial clinical signs (Orzel & Rudd, 1985). The low specificity of the three-phase bone scan can however, lead to potential difficulty in discriminating NHO from other inflammatory, traumatic, or degenerative processes of the skeleton. In addition, bone scanning requires expensive specialist equipment and involves the use of ionising radiation. (Mavrogenis et al., 2011). (Plate 2.3)



Plate 2.3 Bone scan with arrows indicating HO of the hip.

Image source: http://www.physio-pedia.com/Heterotopic_Ossification

2.2.5.2.2 Ultrasound

The use of sonography, as an early diagnostic tool for NHO, has been shown to be both convenient and cost-effective (Falsetti, Acciai, & Lenzi, 2011; Lin, Chou & Chiou, 2014; Pistarini, Carlevati, Contardi & Cannizzaro, 1995; Yeh, Wu, Chen & Wang, 2012). It may also be of use as a simultaneous screening tool for NHO and deep vein thrombosis (DVT) in TSCI patients (van Kuijk et al., 2002). When using ultrasound (US), the intermediate zone initially contains foci of echodense islands and is not uniformly reflective. Later, the foci of echodense islands rapidly merge together and the *complete zone phenomena* can be seen sonographically (Cassar-Pullicino et al., 1993) (Figure 2.7).

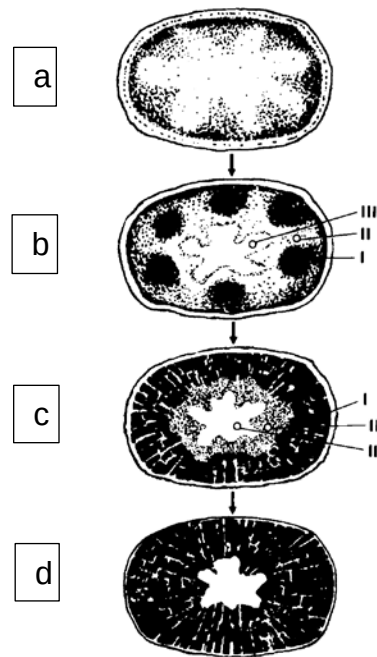


Figure 2.7 Pathology, evolution and maturation of HO.

(a) Peripheral mesenchymal cell stimulation with inward migration towards central core which contains haemorrhage fibrin and necrosis.

(b) 'Zone phenomena' formation: osteoid and bone first laid down in periphery zone I, encompassing the less mature partially mineralised zone II, with immature inner zone III containing active fibroblastic proliferation.

(c) Centripetal maturation with consolidation of the 3 zones to yield.

(d) Mature woven bone with marrow cavity. (Cassar-Pullicino et al., 1993)

As the NHO matures, the peripheral rim of the intermediate zone becomes more reflective on US due to increased mineralization (Cassar-Pullicini et al., 1993; Bodley, Jamous & Short 1993) and from between four to six weeks after the first clinical signs, the NHO begins to behave like corticated bone. At that time, the US beam is totally

reflected and the NHO can also be seen radiographically (Thomas, Cassar-Pullicino & McCall, 1991). Mechanical forces can modify the appearance of the zone phenomena. Therefore, the sensitivity and specificity of US for diagnosing NHO is extremely operator dependent (van Kuijk et al., 2002). (Plate 2.4 A & B)

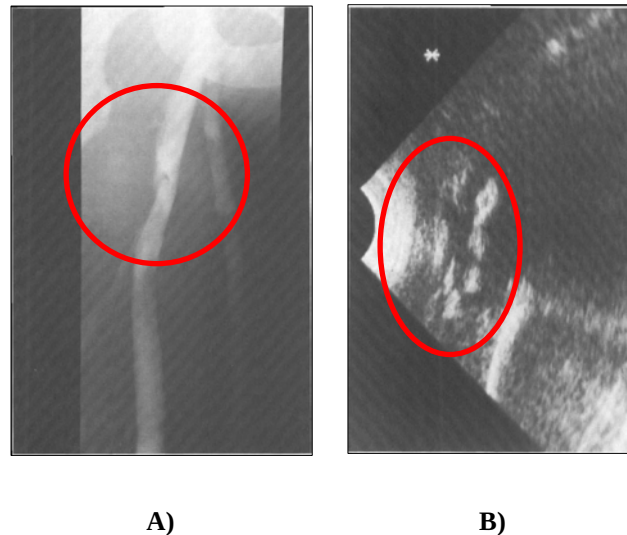


Plate 2.4 A) Extrinsic compression of the femoral vein by HO in the proximal thigh confirmed sonographically. B) (Cassar-Pullicino et al., 1993).

2.2.5.2.3 Radiographs

Radiographs are fast and inexpensive and allow detection of heterotopic ossification approximately four to five weeks after the initial neurological trauma (Orzel & Rudd, 1985). For this reason standard radiography is often the first imaging modality to confirm clinically suspected heterotopic ossification (Seipal et al., 2012). It has been suggested that HO matures through three phases. The early phases are not easily seen on radiographs and the intermediate stage heterotopic bone is poorly delineated from surrounding tissue and shows a more irregular and less calcified internal structure (McCarthy & Sundaram, 2005). With further maturation, the bone becomes better defined and more easily observed on plain X-ray. Calcification density increases and the inner structure becomes more uniform (Seipal et al., 2012). Mature heterotopic bone may also resemble the outer cortical and inner trabecular structure of a normal bone graft (Seipal et al., 2012). In comparison to radiographs, US permits the detection of the initial stages of NHO with comparable sensitivity but offers reduced specificity compared to radiographs for the later stages (Seipal et al., 2012). Radiographs also

permit a standardised quantification of NHO by performing all examinations in standardised planes (Seipal et al., 2012) (Plate 2.5).



Plate 2.5 Radiograph: Arrows indicate NHO around (R) hip in a patient with TBI
NHO= neurogenic heterotopic ossification. (Reznik 2013a)

2.2.5.2.4 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is not routinely used for the evaluation of heterotopic ossification (Mavrogenis et al., 2011). Typical MRIs of heterotopic ossification show a low-signal-intensity rim and a heterogeneous, high-signal-intensity and tumour-like enlargement of affected tissues (Kransdorf, Meis, & Jelinek, 1991), and allow the differentiation of the three distinct stages (De Smet, Meis, & Jelinek, 1992). MRI is, however, more technically demanding and expensive than either US or radiography and lacks specificity, especially in the early phases of NHO, displaying MRI characteristics frequently equated with malignancy (Kransdorf et al., 1991; De Smet et al., 1992) (Plate 2.6).

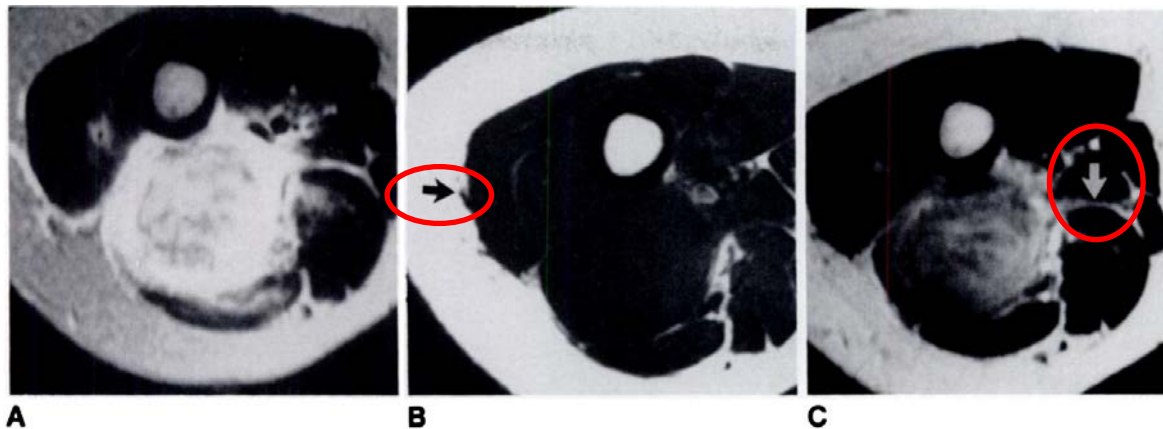


Plate 2.6 MRI scans showing early myositis ossificans in thigh of 24 year old woman with pain for 3-4 weeks.

A) Axial T2-weighted SE MR image (2800/80) shows inhomogeneous, relatively well-designed mass surrounded by diffuse oedema in posterior aspect of thigh. Oedema extends along fascial plane separating muscle from subcutaneous fat.

B) Corresponding axial T1-weighted SE MR image (400/20) shows mass is isointense with skeletal muscle. Area with signal intensity similar to that of skeletal muscle extends into subcutaneous fat laterally (arrow), matching area of increased signal intensity (oedema) on A.

C) Axial T1-weighted SE MR image (400/20) obtained after IV gadopentetate dimeglumine at same level as A and B and shows moderate inhomogeneous enhancement. Oedema is seen enhancing along fascial planes (arrow) (Kransdorf et al., 1991).

2.2.5.2.5 Single-photon emission computed tomography (SPECT)/computed tomography (CT)

Computed tomography (CT) may detect soft tissue ossification at a relatively earlier stage than by standard radiography. Typical CT findings include a low-attenuation soft tissue mass or an enlarged muscle belly, occasionally with indistinct, adjacent soft tissue planes (Bressler, Marn, Gore, & Hendrix, 1987). More recently the hybrid technologies have been used for more appropriate image diagnostics (Lima et al., 2014). The single-photon emission computed tomography (SPECT), in combination with computed tomography multiple cuts (CT) allows the early detection of subtle and non-specific abnormalities on bone scan and interprets them as focal pathology areas (Scharf, 2009). In a recent SPECT/CT study of 12 para/tetraplegic patients with an established clinical diagnosis of NHO, Lima and colleagues (2014) were able to establish a precise anatomical diagnosis of NHO. Moreover, these authors reported that SPECT/CT was able to determine the maturation of HO, showing whether resection would be a safe procedure (Lima et al., 2014) (Plate 2.7).

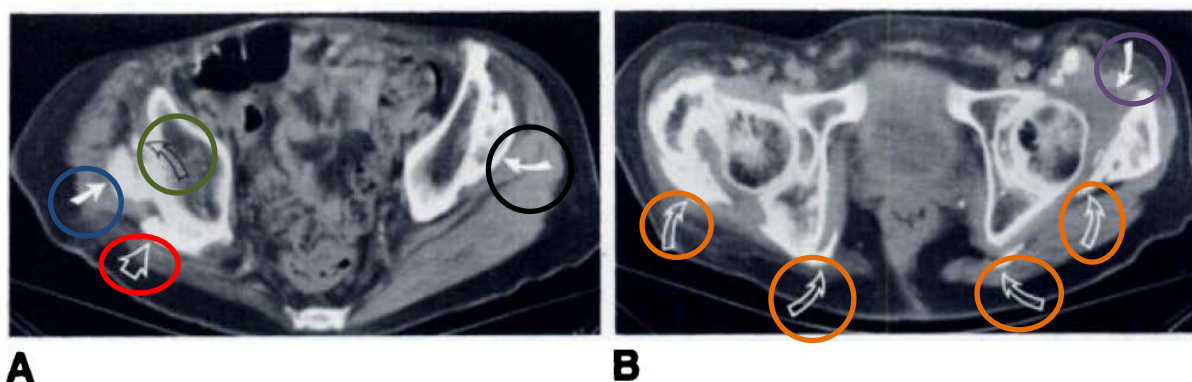


Plate 2.7 CT showing NHO in T10 paraplegic, 10½ years post injury.

A) Ossification between right gluteus maximus and gluteus medius muscles (red circle), between right gluteus medius and gluteus minimus muscles (blue circle), in periphery of right gluteus minimus muscle (green circle), and involving left gluteus minimus muscle and attached to left iliac bone (black circle).

B) Bilateral ossification between gluteus maximus and obturator internus muscles (orange circles). Note low-density soft-tissue material anterior to left hip adjacent to iliopsoas ossification (purple circle) (Bressler et al., 1987).

2.2.6 Management

Currently there are three primary types of NHO treatment used in clinical practice post TBI and post TSCI: pharmacological; non-pharmacological and combined (Aubut et al., 2011; Teasell et al., 2010).

2.2.6.1 *Pharmacological treatments*

Banovac et al (2001) conducted a study on the use of the non-steroidal anti-inflammatory drug (NSAID) indomethacin as a prophylactic medication for NHO after SCI (Banovac, Williams, Patrick & Haniff, 2001). Their results showed a significant reduction in the incidence of NHO in the NSAID-treated patients. Because of the known negative gastrointestinal side-effects of indomethacin, Banovac, and colleagues (2004) conducted a further study on a group of SCI patients with a COX-2 selective inhibitor (rofecoxib), a better tolerated NSAID medication with a lower gastrointestinal toxicity (Banovac, Williams, Patrick & Levi, 2004). This study also demonstrated a decreased incidence of NHO in the treated group (13.4%) as compared with the placebo group (33.3%; $P < 0.05$). These two studies by Banovac and colleagues confirm earlier reports of the beneficial effects of NSAIDs used in the prevention of ‘secondary’ NHO following surgical removal of ‘primary’ NHO (Stover, Hahn & Miller 1991; Charnley, Judet, Garreau de Loubresse & Mollaret, 1996). The mechanism of action of the

NSAIDs in the prevention of NHO is not clear, though inflammation is recognized as an important risk factor for NHO pathogenesis (Banovac, et al., 2004).

Structurally, bisphosphonates are chemically stable derivatives of inorganic pyrophosphate (PPi). Early animal studies from the 1960s showed that PPi was capable of inhibiting calcification by binding to hydroxyapatite crystals which led to the hypothesis that regulation of PPi levels could be the mechanism by which bone mineralization is regulated (Fleisch, Maerki & Russell, 1966; Drake et al., 2008). In humans, bisphosphonates are associated with a potential delay in the mineralization of the osteoid (Fleisch, 2001). There is conflicting evidence as to the effectiveness of the use of bisphosphonates in attenuation of NHO progression (Banovac, Gonzalez, & Renfree, 1997; Speilman, Gennarelli, & Rogers 1983; Stover, Hahn & Miller III, 1976). Speilman et al., (1983) showed that etidronates, a form of the bisphosphonate medications, may be effective in the prevention of NHO in TBI patients. These drugs, however, have not proven to be effective once NHO has developed (Banovac, 2000; Garland, Alday, Venos, & Vogt 1983).

Bisphosphonates in the form of etidronate exert their effects by inhibiting the mineralisation of the bone matrix and not the actual production of the matrix, since the matrix continues to ossify when the drug is withdrawn (Lindholm, Bauer & Rindell, 1986). According to Gallop, Lian & Hauschka (1980) the ossification process of the bone matrix is Vitamin K-dependent, leading to an hypothesis that warfarin, an anticoagulant that decreases the bio-availability of the active vitamin K, may be effective as a prophylactic treatment of NHO (Buschbacher, McKinley, Buschbacher, Devaney & Coplin, 1992). Indeed, anecdotal retrospective observation suggested that TSCI patients treated with warfarin for pulmonary embolus or DVT did not develop NHO (Buschbacher et al., 1992). In the same study, approximately 15% TSCI patients who were not medicated with warfarin developed NHO. Due to the inherent limitations of any incidental observations within a retrospective study, these results must be interpreted with caution. The authors, however, acknowledged that future prospective studies investigating this hypothesis were required.

A more recent study by Scheutz, Mueller, Christ-Crain, Dick & Haas, (2005) reported on the effects of a new generation of amino-bisphosphonates (Pamidronate) on five patients with established HO of varying aetiology, all of whom were about to undergo

surgical removal of their HO. Of the five patients, aged between 47 and 68 years, three had NHO following SCI, one had HO following a total hip arthroplasty (THA) and one had HO due to fibrodysplasia ossificans progressiva (FOP). All five men were treated with continuous pamidronate infusions perioperatively at a dosage of 120 mg in the first 12 hours with subsequent reduction to 75–60–30–15 mg/12 hours over a period of between 10 and 14 days. Follow-up was from four to 54 months post-operatively and none demonstrated radiographic evidence of recurrence, although reappearance of HO in less than six months is unlikely (Mavrogenis et al., 2011). No follow-up surgery was required in any of the patients and no adverse side-effects of the drug were recorded (Scheutz et al., 2005). It is important to note, however, that this small-scale study by Scheutz and colleagues was conducted on a very heterogeneous group of patients and the administration and drug-dosage also varied considerably.

2.2.6.2 *Non pharmacological management*

2.2.6.2.1 Excision

Surgical removal has been advocated by some authors (Garland, 1991a&b; Meiners, Abel, Böhm, & Gerner, 1997; Melamed et al., 2002; Stover et al., 1991) but is extremely invasive and carries with it the possibility of a variety of complications such as post-surgical infections requiring further surgical revisions (Meiners et al., 1997). In addition, earlier studies (Garland, Hanscom, Keenan, Smith, & Moore, 1985; Subbarao, Nemchausky, & Gratzner 1987) suggested that recurrence of the NHO was a further possible post-surgical complication, although in their later study Melamed, et al.,(2002) found no evidence of recurrence in any of their patients. Other less common complications include the formation of a femoral artery aneurysm or superficial pressure ulcers (Meiners et al., 1997). Timing of surgical removal is considered to be critical (Mavrogenis et al., 2011) and should be undertaken only when the NHO is mature. In a recent systematic review of the treatments for NHO following TBI or SCI, Aubut et al., (2011) found that the average time of surgical excision was about 30 months post injury.

2.2.6.2.2 Pulsed low-intensity electromagnetic field (PLIMF) therapy

On the basis of a single randomised controlled trial (RCT), there is evidence to support the efficacy of pulsed low-intensity electromagnetic field (PLIMF) therapy in prophylaxis of NHO after SCI (Durovic, Miljkovic, Brdareski, Plavsic, & Jevtic, 2009).

The authors randomly assigned 29 SCI patients to a control group or a treatment group. Both groups received physiotherapy; however, only the treatment group received PLIMF therapy approximately seven weeks post injury for four weeks. The treatment group showed no incidence of NHO, but a 33% incidence was reported in the control group ($p < 0.04$). Measures were taken only at pre and post intervention and no follow-up was reported. PLIMF therapy uses magnetic fields to increase oxygen levels and decrease the toxic by-products of inflammation by increasing blood flow to the area. No further work on the use of PLIMF has been described.

2.2.6.2.3 Radiotherapy

Radiation therapy has been widely used prophylactically to prevent the development of HO following total hip arthroplasties (THAs) (Ayers, Evarts, & Parkinson, 1986; Ayers, Pellegrini, & McCollister, 1991). Schaeffer and Sosner (1995) described two cases, one TSCI and one TBI patient, with painful NHO around the hip and elbow respectively, who received 10 days of radiation therapy (2 Gy per day for a total of 20 Gy¹). Both patients were pain-free by the completion of the treatments, although follow-up X-rays taken approximately 3 weeks post-treatment did not show any changes in the size of NHO as compared to the pre-treatment radiographs. It would, however, seem unlikely that radiographic changes would be seen so early following treatment. Post-treatment radiological evidence of changes in NHO following other types of interventions for NHO have not been described in less than six months (Buselli et al., 2010; Reznik et al., 2013a).

Sautter-Bihl, Liebermeister, & Nanassy (2000) conducted a study of 36 spinal cord injured patients who received radiation therapy (RT) to 46 joints. Twenty-seven patients were described as having primary incipient HO and eleven patients had manifest ossifications which had to be resected. Two of the 36 patients had both primary and post-operative RT in different joints. Thirty of the 33 patients who were followed up showed no progression of the incipient HO or recurrence of resected bone formations. This study did not include any control group and individual dosages varied considerably. In addition the majority of these patients received this treatment prior to actual clinical significance of HO; therefore it is difficult to establish the actual efficacy

¹ Gray (Gy) is the metric (SI) measurement unit of absorbed radiation dose of ionizing radiation, e.g. X-rays. The gray is defined as the absorption of one joule of ionizing radiation by one kilogram (1 J/kg) of matter, e.g. human tissue

of the RT. Although the authors report no adverse effects, the potential long-term risks of provoking a radiogenic tumour cannot be overlooked.

2.2.6.2.4 Extracorporeal shock wave therapy

Extracorporeal shockwave therapy has been shown over the past ten years to have beneficial effects on a range of musculoskeletal disorders (C-J. Wang, 2012). Two research groups, Brissot et al. (2005) and Buselli et al. (2009) conducted multiple case studies demonstrating that ESWT can also be an effective treatment for HO at the hip and knee. Brissot and colleagues (2005) studied a heterogeneous group of patients with HO and Buselli et al. (2009) studied only young, male athletes with traumatic myositis ossificans in the thigh. Both groups were able to show that four applications of ESWT led to reduced pain, increased range of motion and increased function of the lower limb. A further case of the use of ESWT on myositis ossificans with a similar protocol also produced promising results (Torrence and deGraauw, 2011). As described in Chapter 7, Reznik, et al (2013a) also presented positive outcomes in a single case study on the effect of ESWT on recurrent NHO around the hip of a TBI patient. Although the quality of these studies was good, as assessed by the McMaster Quantitative Critical Review Form (Chapter 4) the limitations due to lack of multiple assessment points, the small sample sizes and the diversity within the forms of HO treated, demonstrates the need for further well-planned studies.

2.2.6.3 Multi-modal approach

In a recent systematic review of NHO interventions post TBI and SCI, Aubut et al., (2011) described nine case series studies, ranging between five and 24 participants, combining pharmacological treatment with surgical resection. The quality of these studies was assessed using a modified Downs and Black quality assessment tool (Downs and Black, 1998) with scores ranging between eight and 15 out of a possible maximum score of 28, indicating that the studies were of low methodological quality (Downs and Black, 1998). The majority of the studies had surgical resection as the primary treatment intervention. In four of the studies bisphosphonate treatment was supplemented with the surgical excision (Fuller, Mark, & Keenan, 2005; Moore, 1993; Scheutz et al., 2005; Subbarao et al., 1987); three studies supplemented the resection with indomethacin (Charnley et al., 1996; Ippolito, Formisano, Caterini, Farsetti, & Penta, 1999; Lazarus, Guttman, Rich, & Keenan 1999); one study supplemented with

both indomethacin and etidronate post resection (Kolessar, Katz, & Keenan, 1996) and one study combined the surgical resection with indomethacin and physiotherapy (de Palma, Rapali, Paladini, & Ventura 2002). Although all of these studies supported the use of combined therapies for the treatment of NHO, all involved surgical resection, which as stated earlier, carries with it the possibility of numerous post-surgical complications.

Fuller et al. (2005) reported on a case series of 17 patients, 15 TBI patients, one with anoxic brain damage and one TSCI patient, who underwent surgical excision of NHO at the knee followed by etidronate treatment given once daily for two months as prophylaxis against recurrence. A significant increase in ROM was documented without clinical or radiographic evidence of recurrence. An earlier case series by Moore (1993) on 17 TBI patients who had surgical excision of NHO in the hips or elbows showed similar results. Each patient was also treated with etidronate postoperatively for up to three months. Thirteen of the 17 patients treated showed an increased ROM which was maintained during the average follow-up period of 23 months. Four patients however had significant post-operative complications either in the form of re-ankylosis (two patients), deep infection (one patient) and delayed wound healing (one patient). De Palma et al., (2002) suggested the importance of active physiotherapy in order to maximise the positive outcomes of the surgical procedure and pharmacotherapy, and noted that the greatest benefit of the combined approach appeared to be highest in the more severely restricted patients. Continuous passive motion (CPM), in addition to surgical excision and indomethacin, was also suggested in retrospective study by Lazerus, et al. (1999). Lazerus and colleagues reviewed 24 TBI patients who had undergone resection of NHO at the elbow. In this study patients who received CPM post-operatively showed a greater improvement in ROM (Lazerus et al., 1999).

All the studies described had limitations in that they were retrospective case series studies without randomization or control groups. In addition to being low level evidence (Straus, Richardson, Glasziou, & Haynes 2005) they did not demonstrate high scores on the quality assessment tool (Downs and Black, 1998).

2.3 Key points

- The initiation and progression of HO appears to be multifactorial with traumatic, neurogenic, systemic, and genetic factors interacting.
- The exact underlying cause of NHO formation following trauma in the central nervous system (CNS) remains unknown.
- Sites of NHO following TBI and/or TSCI are usually around the major joints; the hip, followed by the knee, being the most common site of occurrence.
- The most effective treatment to date for NHO is surgical excision with or without pharmacological intervention, although surgery carries with it many associated complications and the risk of recurrence is considerable.
- Prophylactic methods such as pharmacotherapy or radiotherapy are not effective in reducing the symptoms of established NHO and may carry high-risk side effects.
- In those patients who do develop NHO it is an extremely debilitating complication with serious consequences on their functional abilities.
- Investigation of non-invasive treatment options with minimal associated side-effects is urgently needed; a well-planned prospective study with ESWT is one such alternative.

Chapter 3. Extracorporeal Shock Wave Therapy (ESWT)

3.1 Introduction

Extracorporeal shock wave therapy (ESWT) is a non-invasive method of therapy which uses externally generated high-intensity shock waves to improve chronic, painful conditions of the musculoskeletal system. Shock waves are focused sound waves of microsecond duration with peak pressures between 35 and 120 mega Pascal (MPa) (Chung & Wiley, 2002; Ogden, Tóth-Kischkat, & Schultheiss, 2001; Rompe & Wirth, 2002). Radial ESWT (rESWT) represents an alternative method to focused ESWT. It uses mechanically generated radial shock waves by transforming the kinetic energy of an accelerated projectile into radially expanding shock waves (Gerdesmeyer, Gollwitzer, Diehl, Wagner, 2004). Compared with the ballistic technique to produce shock waves used in rEWST, the focused ESWT sound waves have deeper tissue penetration with higher energies concentrated to a smaller area (Cleveland, Chitnis, McClure, 2007). Despite numerous applications of focused and radial ESWT in orthopaedic conditions, the exact mechanism of physiological effect remains incompletely understood (C-J.Wang, 2012).

ESWT is analogous to lithotripsy, a method used to disintegrate kidney stones without surgery (Drach et al., 1986; Thiel, 2001). It was soon realized that the use of lithotripsy in patients with kidney stones was also associated with the relief of muscular aches and pains (Krishnan Sharma, Singh, 2012; C-J.Wang, 2012).

Valchanou and Michailov (1991) demonstrated the healing effect of ESWT in patients with delayed or non-union fractures with associated analgesic effects. Due to the secondary beneficial effects of ESWT, the probability that shockwaves may have an effect on other types of tissue was examined (McCormack, Jones, McElwain, McHale, & McHale, 1993; McCormack, Lane, & McElwain, 1996; Rompe, Kirkpatrick, Küllmer, Schwitalle, & Krischek 1998). While shock waves in urology (lithotripsy) are primarily used to disintegrate kidney stones, shock waves in orthopaedics (orthotripsy) are associated with neovascularisation, improvement of blood supply and tissue regeneration (C-J. Wang, 2003, 2012). ESWT has been used over the past two decades to treat a wide range of musculoskeletal conditions such as plantar fasciitis, tendinitis and other types of muscle injuries (Seil, Wilmes & Nührenbörger, 2006). It has also

been shown to be effective in treating painful conditions of the larger joints such as the shoulder (rotator cuff injuries) (Wang, Ko, Chen, 2001; C-J. Wang et al., 2003), elbow (epicondylitis or tennis elbow) (Buchbinder et al., 2005; Speed, 2004), hip and knee (tendinitis or "jumper's knee") (van Leeuwen, Zwerver, & van den Akker-Scheek, 2009); the foot being one of the most frequently treated areas (Chuckpaiwong, Berkson, & Theodore, 2009; Crawford, 2005; Furia, 2008). ESWT has also been shown to encourage bone healing and has been used to treat stress fractures, avascular necrosis and delayed or non-union of fracture (Cacchio et al., 2010; Elster et al., 2010; C-J. Wang, 2012). Urological conditions, such as Peyronie's Disease, have also been shown to respond to ESWT (Hauck et al., 2004).

3.2 Physical principles of shockwaves

A shock wave is defined as a sonic pulse and is characterised by high peak pressure (500 bar), a short life cycle (10ms), fast pressure rise (<10ns) and a broad frequency spectrum (16Hz-20MHz). For these very high sound intensities, the wave crest assumes a sawtooth appearance (Figure 3.1).

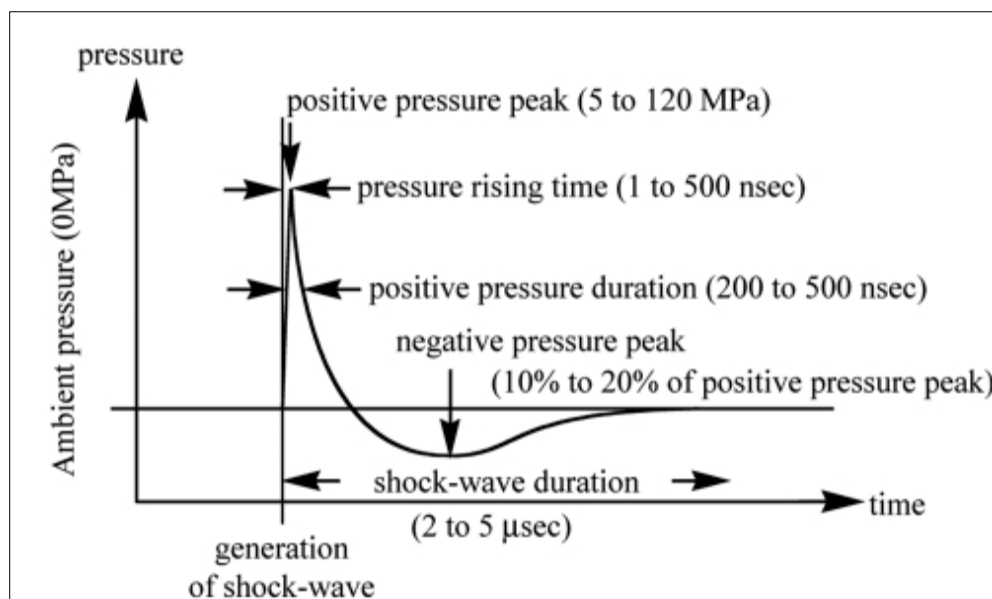


Figure 3.1 Pressure-time curve of a shock wave (Angehrn, et al. 2008).

For clinically applicable shock waves, the pulse energy needs to be focused into areas no larger than 8 mm in diameter in order to optimise the therapeutic effects and minimise the effects on other tissues (Speed, 2004). The site at which the maximum peak-positive acoustic pressure is attained is defined as the focus. The *energy flux*

density (EFD, in mJ/mm^2), is defined as the energy traversing over a small area perpendicular to the direction of the energy flow in a specific time interval, divided by that time interval and by that area. EFD is one of the most important descriptive parameters of the shock wave dosage (Chaussey, Eisenberger, Joachim, & Wilbert 1997; Ogden et al., 2001). ‘High’, ‘medium’ and ‘low’ energy are the commonest classification used to describe the EFD dosage. There is, however no clear consensus of definition for these terms and two classifications have been proposed for EFD (Table 3.1).

Table 3.1

Classification of shock wave therapy according to energy flux density (EFD) range (Speed, 2004).

Authors	Level	EFD range (mJ/mm^2)
Mainz	Low	0.08-0.27
	Medium	0.28-0.59
	High	>0.60
Kassel	*Low	<0.12
	*High	>0.12

Mj/mm^2 , millejoules per millimeter squared

*This is the usual clinical definition used in treatments regimens

3.3 *Methods used to generate shock waves for clinical application*

Three methods based on electrohydraulic, electromagnetic, or piezoelectric principles are used to generate clinically applicable shock waves (Figure 3.2) (Cheing & Chang, 2003; Ogden et al., 2001).

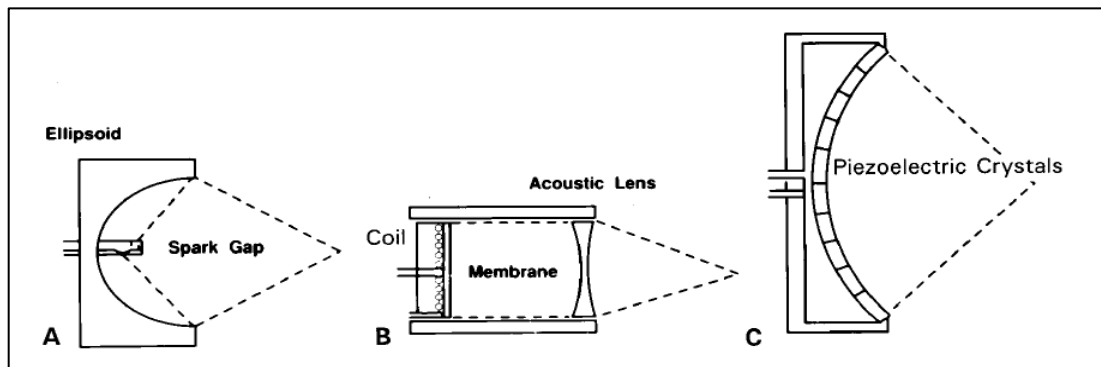


Figure 3.2 The variations in the devices to generate shock waves for clinical application
A) electrohydraulic, B) electromagnetic, and C) piezoelectric (Ogden et al., 2001).

Electrohydraulic shockwaves are high-energy acoustic waves generated by the underwater explosion with high-voltage electrode spark discharge, and the acoustic waves are then focused with an elliptical reflector and targeted at the diseased area to produce therapeutic effect. Electrohydraulic shock wave devices are usually characterised by large axial diameters of the focal volume and high total energy within that volume (Ogden et al., 2001). Shockwave generation through the electromagnetic technique involves the electric current passing through a coil to produce a strong magnetic field. A lens is used to focus the waves, with the focal therapeutic point being defined by the length of the focus lens. The amplitude of the focused waves increases by non-linearity when the acoustic wave propagates toward the focal point (Ogden et al., 2001). Shockwave of piezoelectric origin involves a large number (> 1,000) of piezocrystals mounted on the inside of a sphere. When switching a high voltage pulse to the crystals they immediately contract and expand generating a low pressure pulse in the surrounding water. The geometric arrangement of the crystals causes self-focusing of the waves toward the target centre which leads to extremely precise focusing and high-energy within a defined focal volume (Ogden et al., 2001). In order to improve transmission of the acoustic wave for any of the above types of generation of focused shock waves, it is recommended that a thin layer of ultrasound gel is used as a contact medium between the treatment head and the skin (Cheing & Chang, 2007).

All three mechanisms of producing shock waves result in high EFD. Irrespective of the method of generation, shock waves are concentrated by focusing reflectors on the target

site; increased accuracy can be achieved by the integration of imaging modalities such as fluoroscopy or ultrasound within the treatment head (Speed, 2004).

3.4 Mechanism of shockwave therapy

The mechanism underlying the effect of shockwave therapy in orthopaedic and soft tissue injuries is still not fully understood (C-J. Wang, 2012). The most important physical parameters of shock wave therapy include the pressure distribution, energy flux density and the total acoustic energy. In contrast to lithotripsy in which shockwaves disintegrate renal stones, orthopaedic shockwaves are not used to disintegrate tissue, but rather purported to microscopically cause interstitial and extracellular responses leading to tissue regeneration (Notarnicola & Moretti, 2012).

Studies of the mechanisms underlying ESWT *in vitro* showed that physical shockwave induction of cultured human bone marrow cells could elicit membrane perturbation and reticular activating system (Ras) activation leading to osteogenesis (F-S. Wang, et al., 2001). Wang, and colleagues (2002) conducted further animal studies on four month old male Sprague-Dawley rats and demonstrated that ESWT at high EFDs (0.16 mJ/mm^2) had dose-dependent effects when applied in a range between 250 and 2000 impulses. Bone marrow cells, obtained from rats which had received ESWT, had normal viability in dosages of less than 750 impulses (F-S. Wang, Yang, Chen, Wang, & Sheen-Chen 2002) (Figure 3.3).

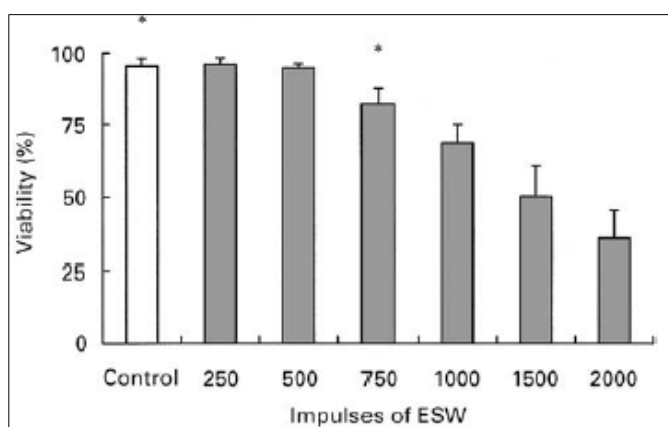


Figure 3.3 Graph showing the effect of ESWT on the viability of rat bone –marrow cells.

***shows significant difference between the effect of treatment with 750 impulses and the control group (F-S. Wang et al., 2002).**

Zhang et al. (2014) also demonstrated *in vitro* this dose dependency effect of ESWT on the formation of new blood cells in ischaemic tissue of Sprague–Dawley rats (Zhang, Yan, Wang, Tang & Chai, 2014).).

3.5 *Bio effects of shock waves*

Potential beneficial effects of focused ESWT on musculoskeletal tissue include direct effects on tissue calcification, alteration of cell activity through cavitation, acoustic micro-streaming, alteration of cell membrane permeability and effects on nociceptors through hyperstimulation, and possible blocking of the gate control mechanism (Table 3.2) (Melzack & Wall, 1965; Speed, 2004).

Table 3.2
Potential mechanisms of beneficial and adverse effects of ESWT (Speed, 2004).

Effects of ESWT	Potential adverse effects	Proposed beneficial effects
Direct tissue trauma and/or cavitation	Bleeding	Stimulation of tissue healing – mechanism unknown
	Production of free radicals	Disintegration of calcium deposits
	Mechanical shearing	Transient inflammatory response
	Ultrastructural damage	
Altered cell membrane permeability	Cell death	Suppression of pain
		Other effects?
Direct effect on nociceptors		Denervation: anti-nociceptor effect
Peripheral nerve stimulation	Arrhythmias, peripheral paraesthesia	Hyperstimulation, blocking gate control mechanism

3.5.1 Stimulation of tissue healing

3.5.1.1 *Animal experiments*

Numerous animal studies have suggested that ESWT stimulates a surge of biological responses, including neovascularisation with associated improvement in blood supply

and tissue regeneration (Chen et al., 2004; C-J. Wang et al., 2002, 2003), bone and cartilage healing (Lyon, Liu, Kubin, & Schwab 2013; Zhao et al., 2012) and cortical bone and callus formation in non-union of fractures (Haupt, G., Haupt, A., Ekkernkamp, Gerety, Chvapil, 1992; Johannes, Sukul, & Matura 1994; C-J. Wang et al., 2001). A study by Forriol et al., (1994) reported that shockwaves had no effect on the periosteal surface of mature cortical bone, although some new trabecular bone was seen on the endosteal surface, suggesting that healing of bone was delayed by ESWT (Forriol, Solchaga, Moreno, & Canadell, 1994). It must be noted that a variety of animals, including rats, rabbits and lambs, were used in these studies as well as a range of EFDs, therefore the clinical implications of these animal studies are uncertain and indeed have been questioned (Perel et al., 2006). Publication bias has also been raised as an issue in many animal studies (Sena, Bart van der Worp, Bath, Howells, & Macleod 2010) suggesting that it may lead to over-estimation of the efficacy of some treatments.

3.5.1.2 *Clinical applications of tissue healing*

ESWT has been utilized for many years in the treatment of a variety of musculoskeletal conditions. A systematic review by Alves and colleagues (2009) discussed five original articles on the treatment of osteonecrosis of the femoral head: two articles were randomised clinical trials, one was an open label study, one a prospective comparative study and one was a case report (Alves, Angrisani, & Santiago, 2009). Outcomes from this review suggested that the original studies had various limitations such as lack of double-blind design, small sample sizes and non-standardisation of the type of shock waves used. Based on positive results provided by previous studies, the authors also recommended further clinical research into the use of ESWT for musculoskeletal pathologies (Alves et al., 2009).

The results of the effects of ESWT in non-union of long bone appear to be promising and comparable to surgical intervention, without the risks associated with surgery (C-J. Wang, 2012). Valchenou & Michailov (1991) reported bony unions after a single dose of high energy ESWT in ~85% of patients with delayed or chronic non-unions of fractures in both upper and lower limbs. This study, however lacked rigor, as there were no controls and the treatment protocol was not standardised. Elster and colleagues (2010) reported on a retrospective analysis of 192 patients treated with high energy

ESWT (EFD of 0.38 to 0.40 mJ/mm²) for chronic non-union of the tibia. The findings of this study suggested that success of the ESWT procedure was inversely related to the number of the pre-ESWT orthopaedic interventions (Elster et al., 2010). It is important to note, however, that retrospective studies are prone to selection bias and potential inconsistencies in reporting outcomes, and in this case, there was no control group without exposure to ESWT. The common limitation of all these original studies was the lack of any mechanistic insights and therefore the exact process underlying cell transformation in humans can only be hypothesised from the animal studies. It would appear that the migration and differentiation of mesenchymal stem cells and promotion of angiogenesis contribute to the increased bone mass and strength (C-J. Wang et al., 2004; F-S. Wang, et al., 2002, 2004).

3.5.2 Disintegration of calcium deposits

ESWT represents mechanical forces that are applied superficially to human tissues. It has been demonstrated that the use of high-dose ESWT regimes were associated with radiological disappearance or disintegration of calcium deposits in calcific tendinitis of the shoulder (Loew, Daecke, Kusnierczak, Rahmanzadeh, & Ewerbeck, 1999). Clinically important secondary effects of high-dose ESWT include mid-term (at least 6 months) effectiveness in pain reduction and consistent improvement in shoulder function in patients with chronic calcific tendinopathy (Table 3.3) (Speed, 2013).

Table 3.3

Studies of Focussed ESWT in the treatment of calcific rotator cuff tendinopathy: 12 week follow-up (unless stated otherwise) (Speed, 2013).

Reference	Design	ESWT type	N	Regime	Result
Cosentino et al., 2003	Single blind RCT	EH	70	4 sessions: 1 session of 12 shocks, 0.03 to 0.28mJ/mm ² 3 sessions of 1200 shocks at 0.28mJ/mm ² (4-7 day interval)	Loss of 2/3 control subjects to follow up at 24 weeks. Significant decrease in pain and increase in shoulder function was seen in the treatment group at the end of Tx and at 1 and 6 month follow-up.
Albert et al., 2007	Single blind RCT	EM	80	2 sessions, 2 week interval: 2500shocks at up to 0.45mJ/mm ²	Benefit in favour of TG at mean follow up 110 days (note significant range; 41-255 days).
Gerdesmeyer, et al., 2003	Multicentre RCT. High vs Low vs Sham	Not stated	144	2 sessions, 12-16 day interval: 1500 shocks at 0.32mJ/mm ² vs 6000 shocks at 0.08mJ/mm ² Same energy in both treatment groups	Benefit in both TG compared to sham at 6 & 12 months, superior in high dose group.

ESWT = extracorporeal shock wave therapy; RCT = randomised control trial;
EH = electrohydraulic; EM =electromagnetic; N = total number of subjects; Tx = treatment; TG=Treatment Group; CG=Control Group; mJ/mm² = millijoules per square millimetre

3.5.3 Suppression of pain

The results of a meta-analysis by Zhiyun et al., (2013) suggested that high-energy ESWT may be effective in reducing pain in recalcitrant plantar fasciitis (Zhiyun, Tao, & Zengwu, 2013). Zhao et al., (2013) carried out a prospective single-blind randomised placebo-controlled trial (RCT) on patients with a diagnosis of primary symptomatic osteoarthritis of the knee. The patient group who received four weeks of high energy ESWT reported a significant decrease in knee pain at four weeks and at the 12 week follow-up as compared to the sham treatment group. The authors reported that ESWT was more effective than the placebo in reducing pain at each period and at 12 week follow-up ($p < 0.01$). A recent systematic review by Speed (2013) on shock wave-based therapies in various soft tissue conditions identified a large number of studies whose principal outcome measure was pain. These include plantar fasciitis (10 studies), insertional (1 study) and mid portion (3 studies) Achilles tendinopathy, calcific rotator cuff/supraspinatus tendinopathy (4 studies), non-calcific rotator cuff tendinopathy (3 studies), and tennis elbow (5 studies). The summarised data indicated that reduction of pain was associated with high- rather than low-dose ESWT (Table 3.4). This conclusion supported previous findings that treatment with ESWT is dose-dependent (C-J. Wang, 2012; Zhang et al., 2012).

Table 3.4
ESWT in Clinical Practice (Effect on Pain) (Speed, 2013).

Good evidence	Some evidence	No evidence	Mixed evidence
Benefit for high dose F-ESWT in plantar fasciitis	Benefit for high dose F-ESWT in mid portion and insertional Achilles tendinopathies	No evidence to support or refute the effects of F-ESWT on other conditions	Mixed evidence for the effects of low dose F-ESWT on common extensor tendinopathies (tennis elbow)
Lack of benefit for low-dose F-ESWT in plantar fasciitis	No benefit for low dose F-ESWT in mid portion and insertional Achilles tendinopathies		
F-ESWT in calcific tendinopathy of the rotator cuff, especially in high doses	Lack of effect of F-ESWT in non-calcific tendinopathy of the rotator cuff and for low dose F-ESWT in tennis elbow		

Levels of evidence defined according to the US Preventative Services Task Force Classification (1989).
F-ESWT= focussed extracorporeal shock waves

The effect of shockwave therapy on patients with complex regional pain syndrome (CRPS) type 1 was investigated by Notarnicola et al., (2010). This was a prospective study on 30 patients with CRPS who received medium-low EFD (0.035 mJ/mm^2) or medium-high EFD (0.09 mJ/mm^2) ESWT according to their pain tolerance. All patients exhibited a significant improvement in their pain scores, as measured by the visual analogue scale (VAS) at the two and six month follow-up visits. Patients also showed a significant functional recovery as measured by the Knee Society Score (KSS) (Insall Dorr, Scott & Scott, 1989). Analysis of the VAS and KSS values according to the EFD applied did not reveal any significant differences between patients who received medium - low and medium – high energy EFD ESWT. Magnetic resonance imaging (MRI) findings at follow up visits demonstrated that in all but one patient there was an evident reduction of the intra-articular swelling in the knee observed pre-intervention. The results of this study suggest that ESWT treatment may be effective in treating CRPS type1 mainly through the modulation of pain, and that improvement from treatment may last for 2-6 months (Notarnicola & Moretti, 2010). However, as this study did not have a control group, the results need to be interpreted with caution.

The biological mechanisms underpinning the efficacy of ESWT in reducing pain in musculoskeletal conditions remain incompletely understood (Speed, 2013). A number of human and animal experiments have been conducted to investigate the analgesic effects of ESWT. Maier et al., (2003) conducted *in vivo* experiments on the distal femur of rabbits. The high energy ESWT was applied randomly to one of the hind limbs with the other hind limb acting as an internal control. The concentrations of substance P (SP), a neurotransmitter involved in perception of pain, extracted from the periosteum of the femur after treatment were measured. The authors reported an increase in the release of SP within the first six hours after application of ESWT, and a decrease six weeks later (Maier, Averbek, Milz, Refior, & Schmitz, 2003). This time course closely approximates that of the clinical time course of an initial increase in pain followed by subsequent pain relief following ESWT application in tendon diseases in humans (Loew et al., 1999). Another study using anaesthetised rats, however, did not find any evidence that SP or calcitonin gene-related peptide (CGRP) production was associated with the application of ESWT (Haake, Thon, & Bette 2002). In contrast, a similar study by Takahashi and colleagues reported an association between the application of low-energy ESWT and decreased levels of CGRP, a potent peptide vasodilator and transmitter of pain, in dorsal root ganglion (DRG) neurons of rats (Takahashi, Wada, Ohtori, Saisu & Moriya, 2003). Ohtori and colleagues (2001) observed almost complete degeneration of epidermal nerve fibres in the shock wave-treated skin of anaesthetised rats. Re-innervation of the epidermis, indicated by the presence of nerve fibres immunoreactive (ir) to the highly sensitive neuronal marker protein gene product (PGP) 9.5, began approximately 2 weeks after the application of shock waves and by day 21 the number of PGP 9.5-ir nerve fibres in shock wave treated skin was not significantly different from that of non-treated skin (Ohtori et al., 2001). (Figure 3.4)

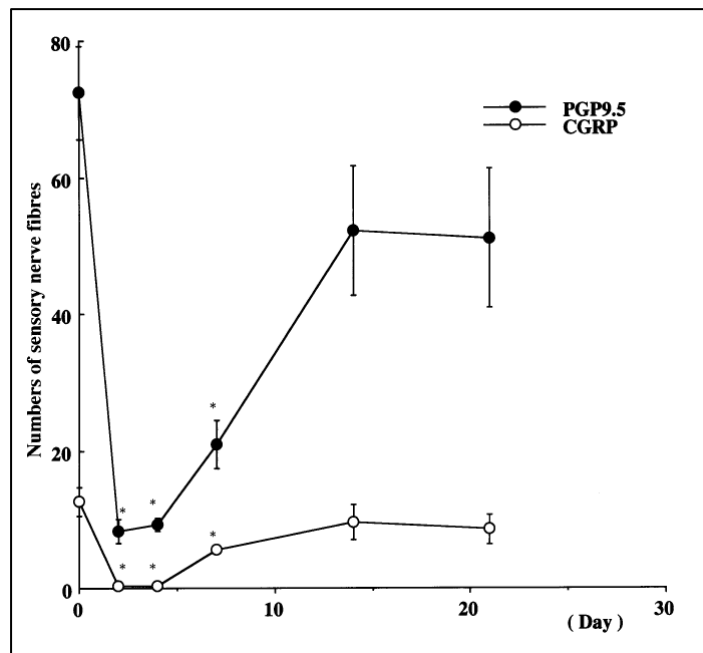


Figure 3.4 The change in number of PGP 9.5-ir or CGRP-ir sensory nerve fibres over time after ESWT treatment.

The number of PGP 9.5-ir or CGRP-ir nerve fibres on day 2, 4, and 7 was significantly less than that of the non-treated skin*. However, on day 14 and 21 no significant differences in these values were observed.

PGP 9.5-ir = protein gene product 9.5-immunoreactive; CGRP-ir = calcitonin gene related peptide-immunoreactive (Ohtori et al., 2001).

A study on anaesthetised rats by Murata et al., (2006) showed ESWT-induced injury of sensory fibres, followed by rapid regeneration of the same fibres. Both small and large diameter fibres were damaged, though a greater proportion of large-diameter fibres were affected. Activity in large-diameter axons is known to modulate nociceptive signals transmitted by small-diameter axons in the dorsal horn (Basbaum & Fields, 1978; Murata et al., 2006). Although a difference in vulnerability between these fibres has not been established (Fröhling, Schlote, & Wolburg-Buchholz 1998), large-diameter fibres are thought to be more sensitive to ESWT than small-diameter fibres (Murata et al., 2006). In this context, Woolf et al. (1992) proposed that the loss of large diameter fibres would lead to increased pain because of the unopposed effects to the small diameter fibres. In addition, damage to large diameter fibres causes them to sprout and expand into the superficial laminae of the dorsal horn, leading to allodynia (Woolf, Shortland, & Coggeshall, 1992). Studies on the analgesic effects of ESWT on a range of musculoskeletal conditions have not described any pain sensitising effects (Speed, 2013; C-J. Wang, 2012).

The actual application of ESWT can be painful (Klonschinski, Ament, Schlereth, Rompe, & Birklein, 2011; Rompe et al., 1997; Wess, 2008). In order to prevent ESWT-related pain, Haake et al. (2002, 2003) used local anaesthesia (LA) at ESWT application sites. They observed that following application of LA, no beneficial effects of ESWT were demonstrated (Haake et al., 2002, 2003).

In a recent study investigating whether LA altered the biological effects of ESWT, Klonschinski et al., (2011) applied focussed ESWT to the forearm skin of 20 healthy individuals, either after topical lidocaine pre-treatment or without on the corresponding contralateral side. This investigation focussed on the ESWT response of the skin, since skin C-fibres are more accessible for functional tests than C-fibres from deep tissues (Klonschinski et al., 2011). The authors also suggested that their results might be generalizable to the peptidergic C-fibres innervating deep somatic structures. During treatment ESWT-associated pain was quantified using an 11-point numerical scale (NRS). Immediately following the application of ESWT the skin-flare was measured by laser Doppler imaging (LDI). Thresholds for painful pinprick sensation were measured using a set of seven calibrated pinpricks (The PinPrick, Mainz, Germany) and pain pressure thresholds were measured using a commercial pressure algometer (FDN 200). In order to control for individual pain susceptibility, both pinprick and pressure pain thresholds were also assessed in control areas on the back of both forearms at least 20 cm apart from the ESWT application. The study showed that ESWT dose-dependently activates and sensitises primary afferent nociceptive C-fibres and that both activation and sensitisation were prevented if LA was applied, indicating that the biological effects of ESWT are significantly impaired if LA is used. These results may explain why the outcomes of clinical ESWT studies in chronic pain differ substantially depending upon the use of LA (Brain & Williams 1988; Haake et al., 2002; Rompe, Meurer, Nafe, Hofmann, & Gerdesmeyer, 2005; Speed, 2004).

Klonschinski and colleagues (2011) put forward three considerations in support of the fact that mechanical stimulation in the form of ESWT activated primary afferent nociceptive fibres: 1) ESWT was painful during application; 2) ESWT induced a neurogenic flare immediately post-treatment; and 3) pressure pain thresholds dropped immediately post-treatment and remained low for a much longer period than the ESWT application. Klonschinski et al. (2011) found only weak indications for ESWT-related

central sensitisation, and in addition they noted the neurogenic flare was more indicative of peripheral sensitisation. They further suggested that activation of the C-fibres caused the release of neuropeptides (Magerl, Wilk, & Treede 1998) whose major role in the periphery is trophic rather than nociceptive. Neuropeptides, in addition to acting upon the microcirculation, also stimulate fibroblasts (Harrison et al., 1995) osteoclastic (Goto, Yamaza, Kido, & Tanaka 1998) and osteoblastic cells (Villa et al., 2000).

The mechanisms leading to the reduction of pain following application of ESWT are still unclear (Speed, 2013). Rompe et al. (1996) suggested that the intense input of the shockwaves activates the small diameter fibres which project to cells in the periaqueductal grey area (Rompe, Hope, Kullmer, Heine, & Burger, 1996). This in turn may activate a descending serotonergic system which ultimately modulates transmission through the dorsal horn. (Melzack, 1975, 1994; Rompe et al., 1996).

Wess (2008) proposed an interesting hypothesis suggesting that ESWT may alter pain circuitry and reorganise the nervous system. This theory has parallels with Melzack's Neuromatrix Theory of Pain (Melzack, 2005), which points towards pain being a product of a widely distributed network in the brain. The neuromatrix concept implies that there are underlying brain mechanisms for some types of chronic pain and offers the suggestion that pain is a multidimensional experience affected by multiple influences. ESWT, acting on small- and large-diameter fibres at the site of application, may therefore lead to lasting changes in the balance of activity in the neuromatrix.

3.5.4 Additional effects of extracorporeal shock wave therapy

In 1999, Gutersohn and Caspari (2000) suggested that low-intensity (LI) ESWT could stimulate the production of new blood vessels from pre-existing ones (angiogenesis). Nishida et al. (2004) investigated the *in vitro* effects of LI-ESWT on human umbilical vein endothelial cells, followed by an *in vivo* study in 28 domestic pigs with induced myocardial ischaemia. On the basis of the results from the *in vitro* experiment they applied LI-ESWT to the ischaemic region of the heart. The authors observed an improvement in myocardial dysfunction associated with the LI-ESWT application and no complications were found either during or after treatment. Using a rat model of chronic hind limb ischaemia, Aicher et al. (2006) demonstrated that pre-treatment of the

ischaemic area with LI-ESWT was associated with an increased number of circulating endothelial progenitor cells (EPCs) to the area, with a resultant significant increase in relative blood flow to the ischaemic tissue ($p < 0.05$). Since there was no randomization these results must be treated with caution and as discussed in a recent systematic review conducted by Sena et al. (2010), “publication bias” i.e. the non-publication of non-significant effects, must also be taken into account.

Clinically, LI-ESWT has been investigated in a number of randomised double-blind controlled studies in human patients with severe ischaemic heart disease (Kikuchi et al., 2010; P. Yang et al., 2013). The studies have suggested that treatment with LI-ESWT led to significantly reduced chest pain symptoms, an increase in the distance walked on the 6-minute walk test and a reduction in the necessity of nitroglycerine use. In an initial exploratory clinical trial with patients suffering from ischaemic heart failure Vasyuk, et al. (2010) demonstrated a significant clinical improvement accompanied by beneficial changes of left ventricular ejection fraction (LVEF) and rest/stress perfusion. The study, however, had a limited number of patients and there was no control group. A later study on patients with coronary artery disease (CAD) by Y. Wang et al., (2012) using cardiac shock wave therapy (CSWT) did, however, incorporate a control group. Their results showed that CSWT improved clinical symptoms, and physiological and functional parameters in CSWT-treated patient with complex CAD compared to untreated CAD patients (Y. Wang et al., 2012). Importantly, all of these studies reported that LI-ESWT was safe without any complications or adverse effects.

A recent review paper by Gruenwald and colleagues (2013) discussed the findings of three small clinical studies they had undertaken on the use of LI-ESWT for erectile dysfunction (ED). Two clinical trials on 49 men showed improvement in ED (Gruenwald, Appel, Kitrey, & Vardi, 2013; Vardi, Appel, Jacob, Massarwi & Gruenwald, 2010) and a third prospective, randomised, double-blind, sham-controlled study on 60 men (Vardi, Appel, Kilchevsky, & Gruenwald, 2012) demonstrated a significant improvement in the International Index of Erectile Function – Erectile Function (IIEF-EF) ($p = 0.0322$). Conflicting results, however, have been reported regarding the efficacy of ESWT in the treatment of Peyronie’s disease (PD), a connective tissue disorder involving the growth of fibrous plaques in the soft tissue of the penis (Gokce, Wang, Powers, & Hellstrom 2013; Skolarikos, Alargof, Rigas,

Deliveliotis, & Konstantinidis, 2005; Srirangam, Manikandan, Hussain, Collins, & O'Reilly, 2006). Currently ESWT is not recommended as a treatment for PD because it has not been shown to improve or stabilize the plaque or penile curvature (Gokce et al., 2013; Hauck, Diemer, Schmelz, & Weidner 2006).

C-J. Wang et al., (2011) investigated the effects of ESWT in induced osteoarthritis (OA) of the knee in rats. The study was a randomised control trial (RCT) involving three groups of rats. Group I were the controls, Group II had induced OA, by transection of the anterior cruciate ligament (ACLT) and no ESWT was applied, and Group III had induced OA and received ESWT to the subchondral bone in the medial tibial condyle 12 weeks after OA had been induced. Post-experimental histological examination of diseased areas demonstrated improvements in bone mineral density and bone strength in Group III as compared with Group II. The conclusions drawn from this study were that a single application of ESWT was associated with regression of ACLT OA of the knees in rats. The effectiveness of ESWT on spinal fusion and callus formation in animals has been established (Ikeda, Tomita, & Takayama 1999; Lee et al., 2008) but biomechanical testing has never been undertaken. Lee et al. (2009) carried out a controlled study of 12, one year old white rabbits who had undergone spinal fusion at the L5-6 level, to test both the effectiveness of ESWT in enhancing the spinal fusion and the residual stiffness of the fused segments. Six rabbits were treated with ESWT and six rabbits were used as controls. The results of this study showed that the application of ESWT was associated with callus formation and increased flexion stiffness ($p < 0.001$) and extension stiffness ($p = 0.0419$), in treated compared to untreated animals (Lee et al., 2009).

C-J.Wang (2012), in his review article on the uses of shock wave therapy, suggested that ESWT may have a use in the treatment of malignant cells i.e. shrinkage of a tumour. Russo et al., (1987) demonstrated that *in vitro* exposure of the Dunning R3327AT-3 rat prostatic carcinoma and SK-Mel-28 human melanoma cell lines to high energy shock waves resulted in a reduction of cell viability. Moreover, when R3327AT-3 cells are exposed to high energy shock waves and subsequently transferred into the rats, a delay in tumour growth was observed (Russo, Mies, Huryk, Heston, & Fair, 1987). In a recent prospective clinical trial, Bae & Kim (2013) assessed the effectiveness of ESWT in the treatment of stage 3 lymphoedema after breast cancer

treatment. The subjective measurements used were hardness of the skin, oedema of the involved upper extremity, and sensory impairment. Each of them was measured by a visual analogue scale (VAS) 0-10, with 10 points being the most severe degree. Objective measurements were the volume of the upper extremity, thickness of the skin, and circumference of the upper extremity. Although the authors found ESWT to be an effective modality in the treatment of lymphatic obstructions following surgical intervention for breast cancer, the study was limited by the small number of participants (n=7), lack of control group and the fact that multiple pre- and post-intervention assessments were not performed (Bae & Kim, 2013).

C-J. Wang and colleagues (2009) in a prospective randomised clinical study, compared the effectiveness of ESWT with hyperbaric oxygen therapy (HBO) in the treatment of chronic diabetic foot ulcers (C-J. Wang et al., 2009). Their results showed that the ESWT-treated patients had significantly better clinical results in terms of local blood flow perfusion, higher cell concentration and activity compared with the HBO-treated patients (C-J. Wang et al., 2009).

Lauer et al. (1997) described shock wave permeabilisation as a new method for delivering gene therapy. The authors demonstrated that upon exposure to shock waves eukaryotic cells displayed a temporary increase in membrane permeability allowing the direct transfer of a naked DNA vector.

Finally, several studies have suggested that ESWT could be used in the treatment of heterotopic ossification (HO)-associated complications associated with a number of conditions including traumatic brain injury (TBI), spinal cord injury (SCI), total hip arthroplasty (THA), and burns (Brissot et al., 2005; Buselli et al., 2010; Reznik et al., 2013a; Torrance and deGraauw, 2011). All four of these studies were limited by selection bias; Brissot et al. (2005) recruited a small sample size (n=26) of participants with diverse conditions; Buselli et al. (2010) findings related only to the specific group tested i.e. young, healthy male athletes. The remaining two studies only reported the outcomes of single cases (Reznik et al., 2013a; Torrance and deGraauw, 2011). The effects of ESWT as a treatment for heterotopic ossification are explored in detail in Chapter 4.

3.6 *Methods of treatment*

No standardised guidelines for the use of ESWT in soft tissue conditions have been proposed. A broad range of regimes with respect to choice of machine, positioning of the patient, localisation of doses, treatment frequencies and the use of local anaesthesia has been employed (Speed, 2013). In an *in vitro* experiment on the endothelial progenitor cells (EPCs) of the bone marrow tissue of 12 Sprague-Dawley rats, Zhang and colleagues (2014) demonstrated a dose-effect relationship of the energy levels of ESWT. This study indicated that shock waves could reduce programmed cell death (apoptosis) when cells were treated with low-energy shock wave and induce apoptosis when cells were treated with high energy shock waves. Accordingly, cell proliferation was observed to be increased at the low energy intensity levels of ESWT, whereas cell proliferation was decreased at the high energy intensity levels (Zhang et al., 2014).

In addition to the number of shocks delivered and the energy flux density (EFD), frequency is another parameter of shock wave therapy that could influence the effects of ESWT. Limited published research exists on the relationship between frequency and the bioactivity of cells, and therefore the relationship between the effect and frequency of shock wave is still uncertain, a fact which may account for the inconsistent findings in the literature (Zhang et al., 2014).

3.7 *Companies manufacturing extracorporeal shock wave therapy devices*

Numerous companies are now producing specialised ESWT devices based on the electrohydraulic, electromagnetic, or piezoelectric principle. Ossatron (Sanuwave/Alpharetta, GA), Orthospec (Medispec, Germantown, MD) and Orbasone (Orthometrix, WhitePlains, NY) are producing electrohydraulic shockwaves; Epos (Dornier Medical System, Kennesaw, GA) and Sonocur (Siemens Medical Systems, Iselin, NJ) are producing electromagnetic shockwaves; and the Piezoson by Wolf produces the piezoelectric shock waves. All of these machines have received FDA approval for use in a variety of conditions and diseases (C-J. Wang, 2003, 2012). As yet there are no published data comparing clinical outcomes of ESWT treatment facilitated by the particular instruments.

Widespread availability of ESWT devices has allowed their application in pre-clinical biomedical research as well as clinically in a range of human musculoskeletal

pathologies. Although there is an abundance of literature available, much has been produced by or under the auspices of companies making the ESWT devices with possible conflicts of interests associated with the outcomes. There is therefore a need for independent, well-controlled studies to be undertaken.

3.8 Key points

- Extracorporeal shock wave therapy (ESWT) is a non-invasive method of therapy which uses externally generated high-intensity shock waves to improve chronic, painful conditions of the musculoskeletal system.
- The *energy flux density (EFD, in mJ/mm^2)* is one of the most important descriptive parameters of the shock wave dosage; low energy ESWT is $\text{EFD} \leq 0.12 \text{ mJ}/\text{mm}^2$, and high energy is $>0.12 \text{ mJ}/\text{mm}^2$.
- Effects of ESWT are dose-dependent.
- Effects of orthopaedic shockwaves are thought to microscopically cause interstitial and extracellular responses leading to tissue regeneration.
- Major biological effects of shockwaves include:
 - Stimulation of tissue healing,
 - Disintegration of calcium deposits, and
 - Suppression of pain.

Chapter 4. Extracorporeal Shock Wave Therapy as a Treatment for Heterotopic Ossification (HO): A Systematic Review and Meta-Analysis of Published Data

4.1 Introduction

The first guiding question in this thesis (Chapter 1) “*what is the evidence for the effectiveness of ESWT in the treatment of NHO in TBI and TSCI patients*” is addressed in this chapter. A systematic review of the literature and a meta-analysis of all available data were undertaken with the aim of clarifying whether ESWT was associated with clinically important improvement in the health status of patients with heterotopic ossification (HO). This paper was published in Physical Therapy Reviews (Reznik et al., 2013b). (Full paper available in Appendix 3B).

4.2 Methods

4.2.1 Literature search

The strategy to identify published studies assessing the use of ESWT for treatment of HO complications was devised according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement (Moher et al., 2009). A systematic literature search was conducted using four electronic bibliographic databases that included the Medline via Ovid, Scopus, CINAHL, and the Web of Science databases. The terms “extracorporeal shock-wave therapy” OR “extracorporeal shockwave therapy” OR “ESWT” AND “heterotopic ossification” OR “HO” OR “myositis ossificans” were used as key terms or Medical Subject Headings (MeSH) where appropriate. Reference lists of selected studies were also hand searched to identify additional publications.

4.2.1.1 Selection criteria

All primary research articles that examined the effect of ESWT on HO or myositis ossificans (MO) in adult humans were included in this review. (MO is an alternative nomenclature for HO). No other limitations were applied, that is, searches were not limited to English language journal articles nor restricted dates of publication.

4.2.1.2 Identification of papers

The author (JER) and a member of her Advisory Panel (SM) independently evaluated the titles and abstracts of the identified studies according to the selection criteria. Thereafter, the full texts of all eligible studies were retrieved and assessed for inclusion or exclusion by the two investigators. Using the 2011 Oxford Centre for Evidence Based Medicine (OCEBM) table, a hierarchical score for the level of evidence was given to each of the retrieved articles. The methodological quality of the included studies was assessed using the McMaster Critical Review Form – Quantitative Studies. In the case of disagreement on a study's eligibility, a decision was made by consensus between the two investigators.

4.2.1.3 Data extraction

The following data were extracted from the included studies using a standardised data extraction form which included: name of first author, year and country of publication, study design, number of participants, patient characteristics, area of body affected, ESWT characteristics and dosage, and before and after ESWT measures taken for function, range of motion (ROM) and pain.

4.2.1.4 Quantitative data synthesis

Since the only recorded movement data found in the literature were hip and knee flexion the analysis was restricted to these data only.

The effectiveness of ESWT for the treatment of HO and/or MO was assessed as the percent improvement in the range of movement (ROM) of flexion at the hip and knee. Percent improvement was calculated for each study using original published data with the formula: Percent improvement = [(post-treatment group mean – pre-treatment group mean) divided by (pre-treatment group mean)] x 100 (Amirfeyz, Pentlow, Foote, & Leslie, 2009). Combined percent improvement in ROM for hip and knee flexion was generated by using a fixed effects model of meta-analysis because of the small number of suitable studies available. Heterogeneity analysis was performed using the Cochran Q test. The association between ROM and pain was assessed by simple linear regression in terms of their respective relative differences. The relative difference was defined as the absolute difference divided by the arithmetic mean of the two numbers whose difference was taken. The relative difference values were natural log-

transformed for analysis. Pearson's correlation coefficient (r) and coefficient of determination (r^2) were also calculated. All computations were performed using the StatsDirect version 2.7.9 statistical software (StatsDirect, Ltd.). Statistical significance was defined at the conventional 5% level. The heterogeneity of the functional outcome measures used across the studies prevented their inclusion in the meta-analysis.

4.3 Results

4.3.1 Selection of studies

Following the PRISMA process for article selection (Moher et al., 2009) (Figure 4.1), a total of five publications were identified by the stated search strategy. After full text screening of the five publications, four articles were selected for inclusion in this review. The fifth article, which was excluded, was a review on HO following total hip arthroplasty (THA) (Stoltny, Koczy, Wawrzynek, & Miszczyk, 2007) and commented only on the study by Brissot et al., (2005), already in the review.

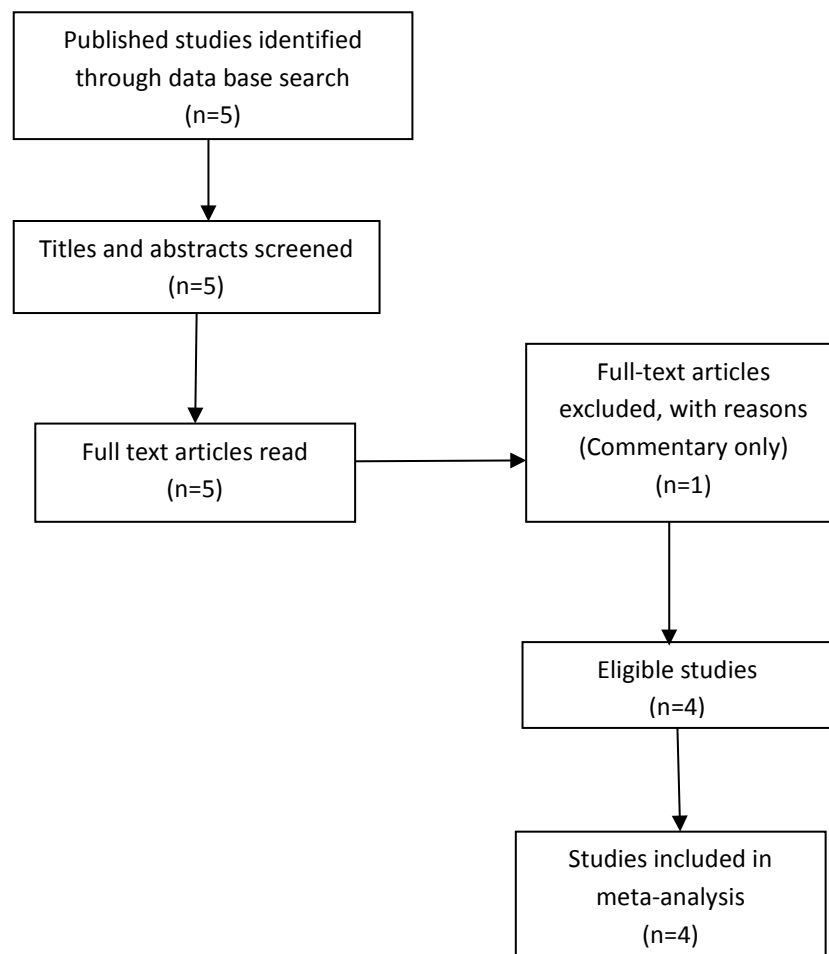


Figure 4.1 Flow diagram showing studies included. (Reznik et al., 2013b)

4.3.2 Characteristics of included studies

All four articles included in this review were either a series of clinical case studies or single clinical case studies. The study by Brissot et al., (2005), a series of clinical case studies, investigated the effects of the application of ESWT on HO around the hip joint in a total of 24 patients of mixed age and with a variety of conditions, including 18 post-THA patients, four traumatic brain-injured patients, one spinal cord-injured patient, one patient with leg trauma, one post-burns patient and one patient who developed spontaneous ossification. The study by Reznik et al., (2013a) was a single clinical case study involving one traumatic brain-injured patient with HO around the hip joint. The studies by Buselli et al., (2010) and Torrance and deGraauw (2011) investigated the effects of ESWT on MO in the quadriceps muscle, affecting knee movements, in a total of 27 young athletes. Follow-up of these case studies varied from no follow-up (Torrance and deGraauw, 2011) to 18 months of follow-up (Brissot et al., 2005) (Table 4.1).

Table 4.1

Characteristics of the four studies included in the review and meta-analysis. (Reznik et al., 2013b)

First author, year of publication and country	Type of study	Area affected	N	Mean Age	EFD	Shocks	No. of Treatment Sessions	LOF (months)
Brissot, et al., 2005 France	Case Series	hip	26	58±16	0.54-1.06	4,000	4	One month post-test Follow-up questionnaire at 11 months to THR participants only (18)
Buselli, et al., 2010 Italy	Case Series	knee	24	27±10	0.13-0.23	2,500	3	1,2.3.6 and 12 months
Torrance & deGraauw., 2011 North America	Case Study	knee	1	20	0.15-0.30	2,500	3	No-follow-up
Reznik, et al., 2013 Israel/Australia	Case Study	hip	1	42	~0.35	3,000	4	5 months

N, Number of individuals; EFD, energy flux density [mJ/mm^2]; Shocks, No. of shocks per session; LOF, Length of follow-up.

4.3.3 Levels of evidence and critical appraisal of studies

The four studies included in this review were either multiple or single case studies and scored a Level 4 on the OCEBM, indicating a low-level of evidence; however using the McMaster Quantitative Critical Review Form, all four articles scored well with scores ranging from 9/14 to 11/14 and 12/14 (Table 4.2).

Table 4.2

Levels of Evidence & Critical Review Form (Potvin, 2007 modified from Law et al., 1998). (Reznik, et al. 2013b)

	Buselli 2010	Brissot 2005	Torrance 2011	Reznik 2013a
*OCEBM Levels of Evidence	4	4	4	4
Was the purpose stated clearly?	Yes	Yes	Yes	Yes
Was relevant background literature reviewed?	Yes	Yes	Yes	Yes
Design (Before and after)	Yes	Yes	Yes	Yes
Was the sample described in detail?	Yes	Yes	Yes	Yes
Was sample size justified?	No	No	No	No
Were the outcome measures reliable?	Yes	Yes	No	No
Were the outcome measures valid?	Yes	Yes	No	No
Intervention was described in detail?	Yes	Yes	Yes	Yes
Contamination was avoided	N/A	N/A	N/A	N/A
Co-intervention was avoided	No – but it remained consistent	No – but it remained consistent	No	No – but it remained consistent
Results were reported in terms of statistical significance?	Yes	Yes	No	No
Were the analysis method(s) appropriate?	Yes	Yes	Yes	Yes
Clinical importance was reported?	Yes	Yes	Yes	Yes
Drop-outs were reported?	Yes, No drop-outs	Yes, No drop-outs	Yes, No drop-outs	Yes, No drop-outs
Conclusions were appropriate given study methods and results	Yes	Yes	Yes	Yes
Overall Score	12/14	11/14	9/14	9/14

N/A – not applicable, *OCEBM –Oxford Centre for Evidence Based Medicine, OCEBM Levels of Evidence Working Group. (2011). The Oxford 2011 Levels of Evidence. Retrieved from Critical Review Form – Quantitative Studies Potvin 2007 modified from Law, Stewart, Pollock, Letts, Bosch, & Westmorland, 1998, from <http://www.uvm.edu/~cdci/tripscy/RevisedQuantReviewForm.doc>.

4.3.4 Characteristics of extracorporeal shock wave treatment modalities

Brissot et al., (2005) used an ESWT machine manufactured by Storz, (Modulith™ SLK); Buselli et al., (2010) generated the ESWT by two electrohydraulic systems, Evotron™ or Ossatron™ (Milano, Italy) OSA 140. Torrance and deGraauw (2011) used the Masterpuls™ MP100 (Storz Medical) and Reznik et al., (2013a) used the Minispec™ Extracorporeal Shock Wave machine (Medispec Int. USA). The energy flux density (EFD), which is considered to determine the power of the shock wave source, was ‘high level’ in each study, according to the Kassel classification (Speed, 2004). The frequency and number of treatments administered were similar. Brissot et al. (2005) gave one treatment a week for four weeks, making a total of four treatments. Buselli et al. (2010) repeated the treatments every two weeks for five weeks, giving a total of three treatments. Torrance and deGraauw (2011) gave three treatments over a 10 day period and Reznik et al. (2013a) repeated the treatments every two weeks over eight weeks, making a total of four treatments. Overall dosages remained similar, although methods of reporting varied slightly. Buselli et al. (2010) and Torrance and deGraauw (2011) following a similar protocol of 100 shocks per cm² of MO. Brissot et al (2005) and Reznik, et al (2013a) reported 4000 and 3000 shocks respectively over the total area of ossification (Table 4.1).

4.3.5 Outcome measures

In all included studies ROM at the affected hip or knee was measured using a universal goniometer and pain intensity was measured using the visual analogue scale (VAS). Buselli, et al. (2010) also recorded reduction of pain using the Fischer algometer score. Functional outcome was assessed by Buselli et al. (2010) and Torrance and deGraauw (2011), as a return to pre-injury status and a return to sport. Brissot, et al. (2005) and Reznik, et al. (2013a) noted an improvement in walking, although using different measures (Table 4.3).

Table 4.3

Outcome measures of the four studies included in the review and meta-analysis. (Reznik et al., 2013b)

First author, year & country of publication	Pain (Visual Analogue Scale)			ROM (in degrees)			Functional outcome Gait/Return to sport		Bone density/ Fischer's algometer		Area of HO on Plane X- ray	
	Before	After	RD	Before	After	RD	Before	After	Before	After	Before	After
Brissot, et al., 2005 France (n=26)	4.32±3.00 (Mean SD)	1.14±2.00 (Mean SD)	0.15	85±31 (Mean SD)	93±31 (Mean SD)	-2.41	1126±1410 Metres (Max. possible distance)	*2776±2040 metres (Max. possible distance)		↓ of ~30% of bone density of the HO in 60% of pts		Unchanged (after one month)
Reznik, et al.. 2013a Israel/Australia (n=1)	9.00	0.00	0.69	85.00	95.00	-2.21	No. steps in 28 metre walk 87	No. steps in 28 metre walk 75	Not meas. [#]	Not meas. [#]		Unchanged (after one month)
Buselli, et al.. 2010 Italy (n=24)	5.40±1.20 (Mean SD)	0.23±0.70 (Mean SD)	0.61	37.10±22.50 (Mean SD)	-6.70±8.50 (Mean SD)	0.33	0	13.5±4.17 (Complete return to sport in weeks)	2.6±1K g/cm ²	4.4±0.9Kg/ cm ²	38.33±13.6 3cm ²	35.54±12.09 cm ² (after 12 months)
Torrance & deGraauw 2011 North America (n=1)	7.00	0.00	0.69	70.00	125.00	-0.58	Not measured ("difficulty in walking")	13 wks post 4Km per day17 wks post 5Km in 25mins	Not meas. [#]	Not meas. [#]	No X-rays taken	

*p<0.05, [#]Not measured , SD, standard deviation; ROM, range of motion (flexion); RD, relative difference (natural log-transformed values); Max, maximum

4.3.6 Quantitative data analysis

In a meta-analysis of data from all four studies there was no significant heterogeneity in results for ROM of the knee (Cochran $Q=0.006$; $P=0.938$) and hip (Cochran $Q=0.009$; $P=0.922$) (Table 4.4). The hip flexion was improved by $> 9\%$ by ESWT at borderline significance ($P=0.086$) using the fixed effects model meta-analysis (Table 4.3). ESWT led to a significant improvement in knee flexion by approximately 82% (95% CI 66.58-96.87; $P<0.001$) (Table 4.4). These results were principally driven by the findings in larger ESWT studies for hip and knee flexion (Figure 4.2a and Figure 4.2b, respectively). There was a positive correlation between ROM and pain relative differences after ESWT with Pearson's $r=0.50$ ($r^2=0.25$). The correlation did not reach statistical significance ($P=0.496$) due to the small number of available studies ($N=4$). (Figure 4.3)

Table 4.4

Meta-analysis of clinical significance of extracorporeal shock wave therapy as a treatment for heterotopic ossification. (Reznik et al., 2013b)

Ossification	Study	N	% improvement of ROM	95% CI	P	% Weight	Cochran Q	df	P
Hip	Brissot, et al. 2005	26	9.41	-1.81-20.63	-	94.41	-	-	-
	Reznik, et al. 2013a	1	11.77	-40.23-51.99	-	5.59	-	-	-
	Combined	27	9.54	-1.36-20.44	0.086	100.00	0.009	1	0.922
Knee	Buselli, et al.. 2010	24	81.84	66.42-97.26	-	96.45	-	-	-
	Torrance & deGraauw 2011	1	78.57	-1.85-158.99	-	3.55	-	-	-
	Combined	25	81.72	66.58-96.87	<0.001	100.00	0.006	1	0.938

N, Number of individuals; ROM, range of motion (flexion); 95% CI, 95% confidence interval; P, P value; df, degrees of freedom

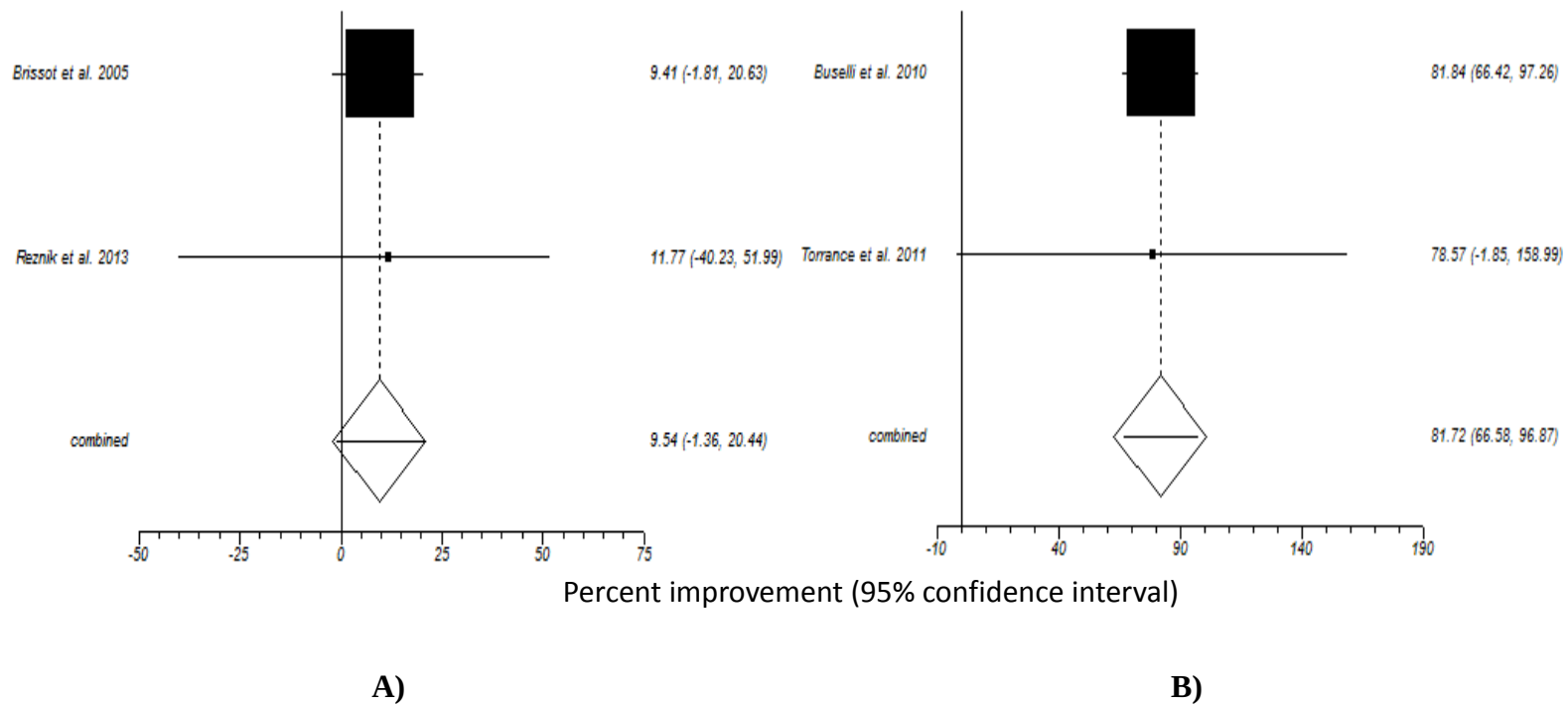


Figure 4.2 Forest plots detailing percent improvement in range of motion for hip (a) and knee (b) flexion.
The dotted line represents overall percent improvement calculated in the current meta-analysis. (Reznik et al., 2013b)

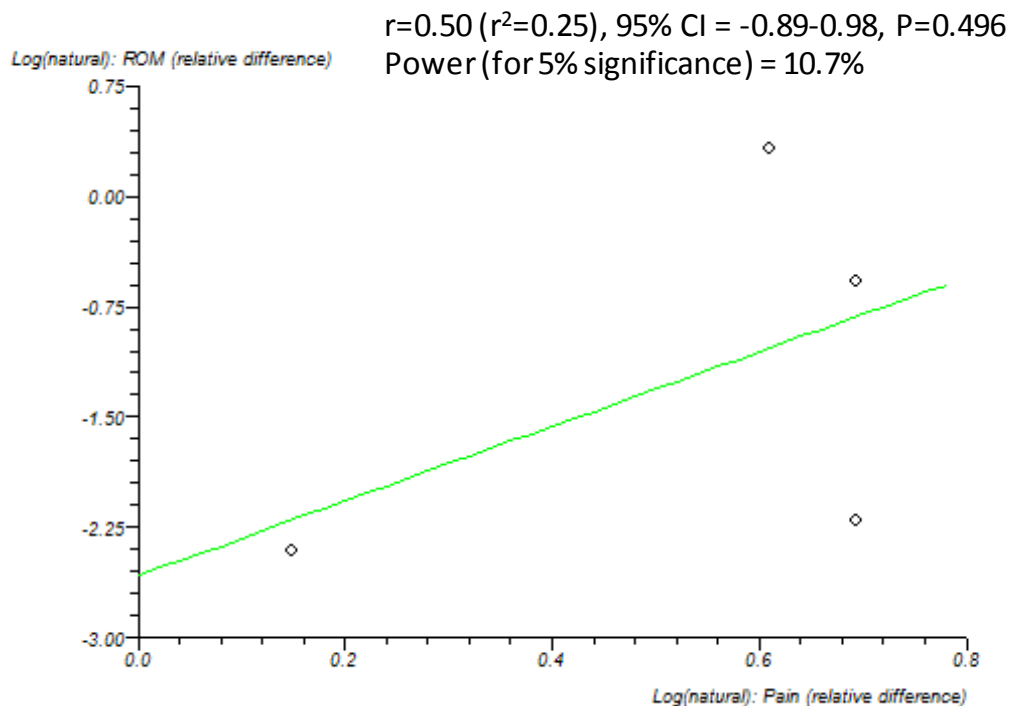


Figure 4.3 Scatter plot with regression line for association between ROM and pain after ESWT. (Reznik et al., 2013b)

4.4 Discussion

This is the first systematic review to summarise the evidence on the use of extracorporeal shock wave therapy to relieve pain, increase range of motion and improve function in people with heterotopic ossification or myositis ossificans. Each of the four papers reviewed suggested that the application of ESWT may have a positive effect on the outcomes assessed.

Other treatment options which may be considered for HO and/or MO include pharmacotherapy, electromagnetic intervention, radiotherapy and/or surgery. These treatment options are discussed in detail in Chapter 2 (Heterotopic Ossification) and the possible side effects with all these interventions are also considered. In contrast, three out of the four papers in this study, reported no side effects at all post-ESWT, and the fourth paper reported only 12 hours of muscle soreness.

The potential adverse side effects of ESWT are discussed in Chapter 3 (Extracorporeal Shock Wave Therapy).

4.4.1 Biases across all and/or individual studies

All four included studies showed selection bias. Brissot et al., (2005) had a wide heterogeneity of participants, with an uneven distribution of conditions and a relatively small sample size. Buselli et al., (2010) acknowledged that their findings relate only to the specific group tested i.e. young, healthy male athletes. The remaining two studies (Torrance and deGraauw, 2011; Reznik et al., 2013a) were single case-studies and were therefore, by definition, potentially biased.

The McMaster Critical Review Tool used in this review, established that the quality of the published information was good. However, since no control group was used in any of the four studies it would be difficult to ascertain if the treatment effect was secondary to a placebo effect or maturation bias. In addition, three out of the four papers used the visual analogue scale (VAS) as an outcome measure of pain intensity; pain is a subjective experience therefore the VAS may not always be recognized as a truly objective measure (Kramer, et al. 2012). HO, however, is likely to lead to chronic pain, which is understood to be the result of changes throughout the nervous system. The International Association for the Study of Pain (IASP) defines pain as a subjective experience, and therefore scales such as the VAS are reported to be valid (Merskey & Bogduk, 1986).). Finally, although the use of a universal goniometer has been shown to be reliable (Gajdosik & Bohannon et al., 1987) measurement of ROM using this device is subject to measurement error. If the difference is small ($<5^{\circ}$) the margin of error may be greater than the improvement measured (Rothstein, Miller, & Roettger et al., 1983).

It must also be taken into account that different types of HO were being treated, and possible differences in the underlying mechanisms for each type and subsequent variations in their response to ESWT, could also lead to confounding bias.

Therefore, although the studies imply positive effects of treatment with ESWT on pain and ROM, the bias associated with the lack of a control group, the lack of random allocation to the experimental treatment, small sample sizes and the diverse forms of HO being treated means that the true effect of ESWT cannot yet be determined.

As previously stated, ESWT is currently being used therapeutically in a variety of musculoskeletal conditions such as delayed or non-union of fractures (Alvarez et al., 2011; McKee, 2010; W. Wang & He, 2005), calcifying tendinitis (Albert et al., 2007),

epicondylitis (Chung & Wiley, 2004) and plantar fasciitis (Ogden et al., 2004). In the current meta-analysis available data were combined from the four studies assessing the efficacy of ESWT in the treatment of painful and debilitating conditions associated with post-traumatic HO. The analysis suggests clinically significant improvement in ROM at the hip and knee joints after ESWT. It should be noted that these findings were principally driven by the two larger studies (Brissot et al., 2005 and Buselli et al., 2010), one study assessing knee flexion and the other assessing hip flexion.

Much of the attention to date has focused on the effects of ESWT in managing pain (Buchbinder et al., 2006; Rompe, 2006; Wess, 2008). The current study suggests the effectiveness of ESWT in reducing pain, increasing ROM and improving function in patients with differing types of HO. The findings, however, imply that only 25% of the positive improvement in ROM can be attributed to alleviation of pain, suggesting that ESWT may trigger other mechanisms contributing to positive clinical outcomes. Previous studies have provided evidence that application of ESWT was associated with a reduction, on plane X-ray, in the area of ossification and decrease of density in bone-like structures (Brissot et al., 2005; Buselli et al., 2010). This might be mediated by the development of inflammation as a result of mechanical forces (Hazan-Molina, Kaufman, Reznick, & Aizenbud 2011) however, further examination in other contexts, such as animal models, is needed to support this hypothesis.

4.4.2 Limitations of the study

The number of studies meeting the selection criteria for inclusion to the meta-analysis was small and limits the generalisability of the findings. Furthermore, available comparable data were found only for hip and knee flexion. The findings from this study therefore, do not relate to the total range of available joint motion. Finally, the majority of patients were young individuals, limiting the relevance of the findings for individuals of advanced age.

McCarthy & Sundaram (2005) hypothesised that four factors are necessary in the pathogenesis of heterotopic bone: an inciting event, a signal from the site of injury, a supply of mesenchymal cells whose genetic machinery is not yet fully committed and the appropriate environment conducive to the continued production of the heterotopic bone. This hypothesis is further examined in the possible causative factors in the

development of HO in Chapter 2. In examining the diversity of patients who are at risk in developing HO it may be more appropriate to examine separately different types of HO, i.e. genetic, neurogenic, post-traumatic, post-surgical and “reactive” causes of HO (McCarthy & Sundaram, 2005).

At this stage randomised double-blind controlled trials with sham ESWT are required to determine the effectiveness of ESWT as a therapeutic intervention for HO. However, because the number of patients with specific types of HO is relatively low, randomised controlled trials may not be feasible. Within-subject designs such as “pre-post” and single case designs, especially if extended baseline and post-treatment observations were included, could also add valuable information to the current literature. It has been noted that in some cases, observational studies give the ‘best’ evidence (Aronson & Hauben, 2006) and there is now a growing recognition that observational studies – such as case-series (Glasziou, Chalmers, Rawlins, & McCulloch 2007) *and anecdotes* can sometimes provide definitive evidence (Aronson & Hauben, 2006).

4.5 Key points

- Four articles of low evidence score met the inclusion criteria for this systematic review.
- ESWT led to an improvement in knee flexion by ~ 82% and hip flexion of ~10%.
- Only 25% of relative improvement in ROM can be attributed to the alleviation of pain after ESWT.
- ESWT may be associated with clinically significant improvement of ROM of lower extremities in patients with HO.

Chapter 5. Prevalence and Risk-Factors of Neurogenic Heterotopic Ossification (NHO) in Traumatic Spinal Cord Injured (TSCI) and Traumatic Brain Injured (TBI) Patients admitted to Specialised Units in Australia

5.1 Introduction

The second guiding question in this thesis (Chapter 1) “*what is the prevalence of NHO in TBI and TSCI patients in specialised units?*” is addressed in this chapter. In order to identify patients with a high-level risk of developing NHO after traumatic brain and spinal cord injuries, and to determine the prevalence of NHO in these patient populations, an audit was carried out of the records of patients admitted to specialised units at the Hampstead Rehabilitation Centre in Adelaide, Australia. This paper was published in the Journal of Musculoskeletal Interactions (Reznik et al., 2014) (Full paper available in Appendix 3C).

5.2 Materials and methods

Ethics approval for this audit was granted by the Royal Adelaide Hospital Human Research Ethics Committee (RAH PROTOCOL NO: 121124) and from James Cook University (H4943).

5.2.1 Identification of patients

TBI and TSCI patients were identified using the Open Architecture Clinical Information System used at the Hampstead Rehabilitation Centre (OACIS). This OACIS system enables data to be gathered from different clinical systems and uploaded into a central repository. The separation summaries and clinical reports of all patients admitted to the Spinal Injury Unit and Brain Injury Unit at the Hampstead Rehabilitation Centre in Adelaide, Australia, between January 2007 and December 2012 were identified.

The diagnosis of NHO in TBI and TSCI patients was made only when NHO became a clinically significant condition. The screening protocol for TBI and TSCI patients

admitted to the specialised units at HRC included physiotherapy assessments and medical imaging.

Physiotherapy assessments as per standard care included:

1. Measures of passive range of motion (ROM) in upper limbs (UL) and lower limbs (LL) performed unilaterally and bilaterally at a minimum of weekly intervals.
2. Recorded or self-reported measures of spasticity in terms of mild, moderate or severe (UL, LL, truncal).

The presence of one or more of the following signs indicated the possibility that NHO was present:

1. An objective decrease of more than 5 arc degrees (°) in passive ROM from previous assessment;
2. An increase in severity of spasticity from the previous assessment;
3. Inflammatory signs at the hip/pelvis such as redness, heat, and swelling;
4. Abnormal joint “end feel” on passive ranging (flexion/abduction hip).

Clinical suspicion of NHO, i.e. the presence of one or more of the above signs and symptoms, was confirmed or excluded by radiography using the technetium whole body bone scan (Seipal et al., 2012)

5.2.2 Audit protocol

The audit protocol adopted was originally developed by Goldman (1980) and modified according to more recently published literature (Cipriano et al., 2009; Sakellariou et al., 2012; Teasell et al., 2010; van Kampen et al., 2011). The retrospective audit was conducted between February and August 2013 and clinically relevant characteristics, as previously identified from the literature, were manually extracted and recorded in a Microsoft Excel spread sheet Where information was missing or sparse the treating physician or physiotherapist was consulted. The list of all variables recorded is shown in Table 5.1.

Table 5.1
Variables recorded. (Reznik, et al. 2014)

Variable		TBI	TSCI
Patients (number)		262	151
NHO (number)		10	16
Combined (number)		11	
Date of injury		√	√
Age at time of injury		√	√
Gender		√	√
ISNCSCI		X	√
AIS		X	√
GCS		√	X
Length of time in PTA		√	X
Presence of NHO /number of joints affected		√	√
Presence of DVT/PE		√	√
Presence of UTI		√	√
Presence/ number of Pus		√	√
Presence of spasticity		√	√
Mechanical ventilation		√	X
Co – morbidities	Respiratory disorders	√	√
	Cardiovascular disorders	√	√
	Orthopaedic disorders	√	√
	Chronic pain	√	√
	Psychiatric disorders	√	√
	EtOH abuse	√	√
Length of stay in unit		√	√
Mode of separation		√	√
Nursing/Physiotherapy Management		√	√
Blood characteristics	Albumin (g/L)	√	√
	WCC (10 ⁹ /L)	√	√

TBI: Traumatic Brain Injury, TSCI: Traumatic Spinal Cord Injury, ISNCSCI: International Standard Neurological Classification of Spinal Cord Injury, DVT: Deep Vein Thrombosis, PE: Pulmonary Embolus, AIS: ASIA Impairment Scale, UTI: Urinary Tract Infection, GCS: Glasgow Coma Scale, PU: Pressure Ulcer, PTA: Post Traumatic Amnesia, EtOH: Ethanol, NHO: Neurogenic Heterotopic Ossification, WCC: White Cell Count.

Recorded data were subsequently statistically analysed to identify TBI and TSCI patients at high risk of developing NHO. A priori risk factors in the development of NHO in TSCI and TBI patients respectively, are as documented in Tables 5.2 and 5.3.

Table 5.2
Risk Factors for Developing Neurogenic Heterotopic Ossification (NHO) in TSCI patients (Reznik et al., 2014)

Risk Factors	Goldman, 1980 (n=738)	Coelho & Beraldo, 2009 (n=230)	Reznik et al., 2014 (n=151)
Gender	M	M	M >F
Age	20-40	Not documented	31.4±10.9 years
Level of Injury	Thoracic lesion	Thoracic lesion	Not significant
Complete/Incomplete	**Complete	**Complete	***AIS B
Spasticity	Absent/Mild	Absent/Mild	Not significant
Pressure Ulcers	Present	Present	Multiple pressure ulcers
DVT	No	No	Significant
Length of Stay	>6 weeks	Not documented	207±175 days
Type of injury	RTA	Not documented	RTA
Smoking	Not documented	No	Not significant
Urinary complications	Not documented	Present	Significant

M=Male; F= Female; AIS = ASIA Impairment Scale; RTA= Road Traffic Accident

As per Frankel Scale (Appendix1A), * see AIS Scale (Appendix 1B)

Table 5.3

Risk Factors for Developing Neurogenic Heterotopic Ossification (NHO) in TBI patients. (Reznik et al., 2014)

Risk factors	Simonsen, 2007 (n=114)	Van Kampen, 2011 (n=97)	Reznik et al., 2014 (n=262)
Gender	M =F	M >F	M=100%
Age	Median 23 years	Median 35 years	39.6±15.5 years
Spasticity	Severe	Absent/mild	Severe
Length of Stay	Median 192 days	Not documented	143±117 days
Immobilisation	Yes	Not significant	Not documented
SAP levels	Raised	Not documented	Not documented
Mechanical ventilation	Not documented	Mean 16.50 days	Significant
Autonomic dysregulation	Not documented	Significant	Not documented
Long bone fractures	Not documented	Not significant	Significant

M=Male; F= Female; SAP= Serum Alkaline Phosphate

5.2.3 Statistical analysis

Univariate association of continuous and nominal covariates with NHO was examined by the Mann–Whitney U test and Fisher’s exact test, respectively. Our binary outcome was the presence of NHO in patients with TBI or TSCI. Logistic regression was used to model the effects of multiple covariates on binary outcome and results were presented as odds ratio (OR) with its 95% confidence interval (95% CI). Statistical significance was defined at the conventional 5% level. All computations were performed using the SPSS statistical package v.20.0.0.

5.3 Results

The OACIS tool identified 262 TBI patients, 151 TSCI patients, and 11 patients with a combined head and spinal cord injury admitted to the Hampstead Rehabilitation Centre between January 1 2007 and December 31 2012. The 11 patients with combined head and spinal cord injuries were considered to be confounders and were removed from

further analyses. NHO was diagnosed in 10 and 16 patients with TBI and TSCI, respectively (Table 5.1). Eighteen clinically relevant characteristics were recorded and analysed for the association with NHO in TBI and TSCI patients (Table 5.1).

5.3.1 Mode of injury in patients with TBI and TSCI

The most common modes of injury, accounting for more than 50% of all identified TBI and TSCI patients, were falls (TBI=23.66%, TSCI=18.54%), driver or passenger motor vehicle accidents (TBI=22.90%, TSCI=27.81%), and motorbike accidents (TBI=17.89%, TSCI=18.54%), (Figure 5.1). TBI, compared to TSCI, was significantly more associated with assaults (15.64% vs. 0.66%, $P<0.001$) and pedestrian accidents (8.78% vs. 0.66%, $P<0.001$). On the other hand TSCI as compared to TBI was significantly more associated with sporting accidents (TSCI=11.92%, TBI=1.91%, $P<0.001$), industrial or work related accidents (TSCI=5.96%, TBI=0.00%, $P<0.001$), and accidents associated with flying activities (TSCI=2.65%, TBI=0.00%, $P=0.017$).

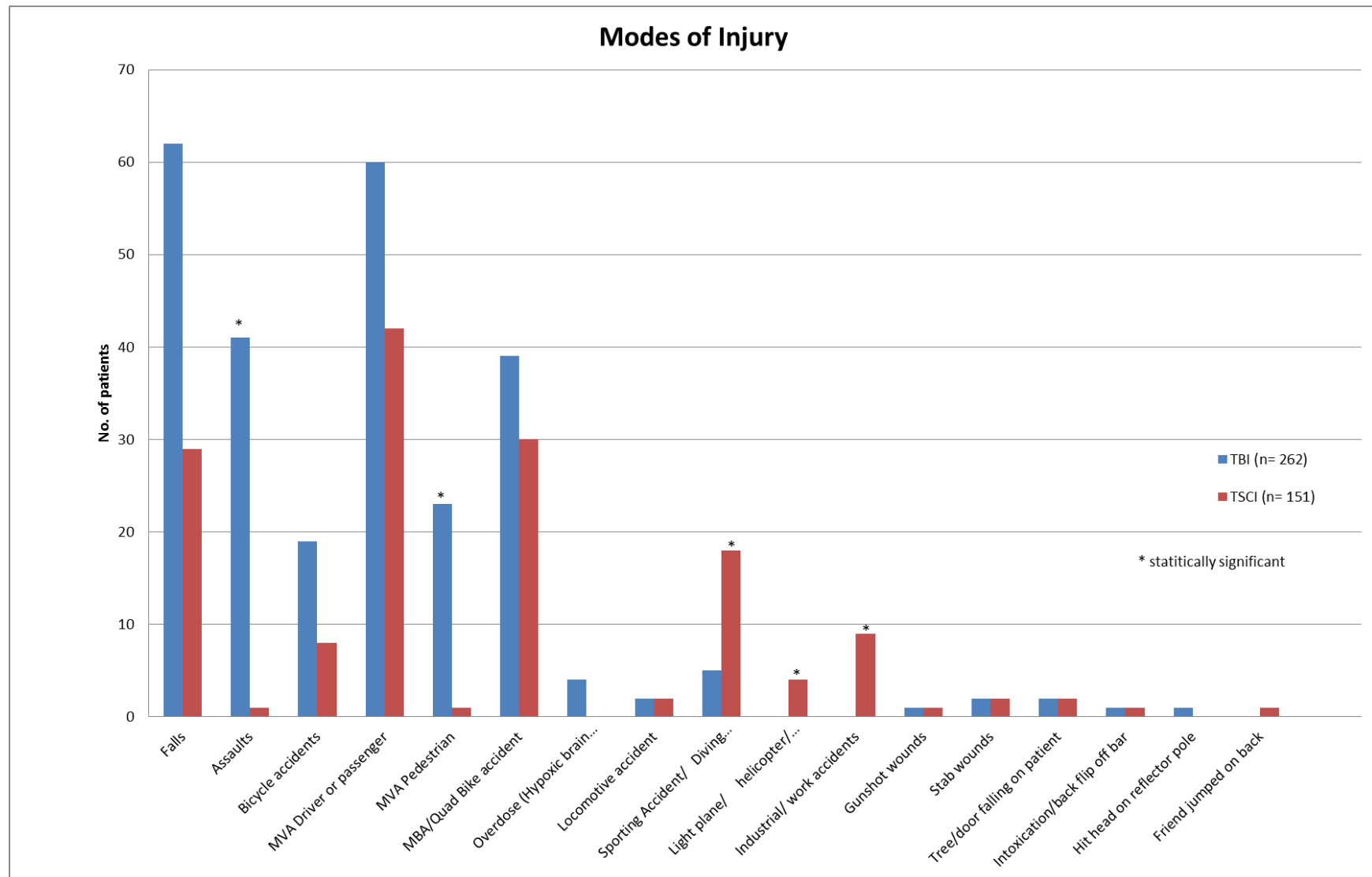


Figure 5.1 Bar graph showing the numbers of patients with TBI and TSCI according to the mode of injury.

TBI= Traumatic Brain Injury; TSCI= Traumatic Spinal Cord Injury; MVA =motor vehicle accident; MBA = Motorbike accident; n= number of patients; *statistically significant difference. (Reznik et al., 2014)

5.3.2 Diagnosis of NHO in patients with TBI and TSCI

NHO was diagnosed when it became clinically significant by radiography using the technetium whole body bone scan (Seipal et al., 2012). All TBI and TSCI patients who developed clinically significant NHO had decreased ROM at the affected joint by at least 5°.

5.3.3 Sites of NHO in patients with TBI and TSCI

Both groups developed NHO most commonly in the hip joint. The elbow was involved significantly more often in TBI patients than TSCI patients (Table 5.4).

Table 5.4
Sites of NHO. (Reznik et al., 2014)

	Joint	TBI-HO (n=10*)	TSCI-HO (n=16*)	P
Shoulder	Unilateral	0 (0%)	0 (0%)	-
	Bilateral	0 (0%)	1 (6%)	>0.999
Elbow	Unilateral	3 (30%)	0 (0%)	0.046
	Bilateral	0 (0%)	0 (0%)	-
Hip	Unilateral	4 (40%)	10 (63%)	0.301
	Bilateral	0 (0%)	3 (19%)	0.215
Knee	Unilateral	3 (30%)	1 (6%)	0.157
	Bilateral	0 (0%)	1 (6%)	>0.999

NHO = Neurogenic Heterotopic Ossification; TBI-HO = Traumatic Brain Injury with Heterotopic Ossification; TSCI-HO= Traumatic Spinal Cord Injury with Heterotopic Ossification; *n = number of patients with clinically significant NHO (some patients had more than one site affected)

With regards to the sites of NHO, elbows were unilaterally affected in TBI patients rather than TSCI patients (30% vs. 0%, P=0.046; Table 5.4). However, NHO developed unilaterally more often in the hip area in TSCI patients than TBI patients (63% vs. 40%), though the difference did not reach statistical significance (P=0.301; Table 5.4).

5.3.4 Risk factors associated with NHO in patients with TBI and TSCI

An analysis of clinically relevant variables in TBI and TSCI patients was performed in order to assess their association with NHO. The prevalence of NHO in TBI patients was

found to be about one-third of that found in TSCI patients, 4% and 11%, respectively (Table 5.5). The only variables that appeared to be commonly associated with NHO in both neurological conditions were deep vein thrombosis and/or pulmonary emboli (DVT/PE). The prevalence of DVT/PE in TBI patients with NHO was 40% compared to 6% in TBI patients without NHO ($P=0.004$). The prevalence of DVT/PE in TSCI patients with and without NHO was 25% and 6%, respectively ($P=0.025$; Table 5.5). Certain variables appeared to be exclusively associated with NHO in TBI or TSCI patients. In the TBI group of patients these include spasticity, period of intubation, urinary tract infections, multiple injuries and the length of stay (Table 5.5). In the TSCI group, patients with NHO, compared to patients without NHO, showed a significantly higher prevalence of multiple pressure ulcers and AIS B (ASIA Impairment Scale, Appendix 1B) (Table 5.5). It should be noted however, that TSCI patients (AIS D, i.e. sensory and motor incomplete) with NHO as compared to patients without NHO showed significantly less prevalence of NHO (Table 5.5).

Table 5.5

Univariate analysis of patients with and without NHO after Traumatic Brain and Spinal Cord Injuries. (Reznik et al., 2014)

Characteristic		TBI			TSCI		
		NHO	No NHO	P	NHO	No NHO	P
N		10 (4%)*	252 (96%)	-	16 (11%)*	135 (89%)	-
Age (years)		39.6±15.5	39.9±16.2	0.852	31.4±10.9	38.1±17.5	0.288
Male		10 (100%)	216 (86%)	0.366	13 (81%)	115 (85%)	0.713
Female		0 (0%)	36 (14%)	0.366	3 (19%)	20 (15%)	0.713
ISNCSCI level	Cervical	-	-	-	11 (69%)	68 (50%)	0.177
	Thoracic	-	-	-	5 (31%)	49 (36%)	0.715
	Lumbar	-	-	-	0 (0%)	10 (7%)	0.314
	Cauda Equina	-	-	-	0 (0%)	8 (6%)	0.399
	A	-	-	-	8 (50%)	53 (39%)	0.422
AIS score	B	-	-	-	6 (38%)	16 (12%)	0.017
	C	-	-	-	1 (6%)	19 (14%)	0.430
	D	-	-	-	1 (6%)	39 (29%)	0.046
	E	-	-	-	0 (0%)	1 (1%)	0.894
	Central cord lesion	-	-	-	0 (0%)	5 (4%)	0.567
	Hemi-section of cord	-	-	-	0 (0%)	2 (1%)	0.799
Lowest	Nil/not noted	2 (20%)	63 (25%)	0.773	-	-	-
GCS at time of injury	Mild	2 (20%)	59 (23%)	0.857	-	-	-
	Moderate	0 (0%)	44 (18%)	0.154	-	-	-
	Severe	6 (60%)	86 (34%)	0.116	-	-	-
	No	4 (40%)	121 (48%)	0.640	-	-	-
Length of PTA (days)	Mild	0 (0%)	0 (0%)	-	-	-	-
	Moderate	0 (0%)	3 (1%)	0.889	-	-	-
	Severe	0 (0%)	14 (6%)	0.572	-	-	-
	Very severe	6 (60%)	114 (45%)	0.382	-	-	-

Characteristic		TBI			TSCI		
		NHO	No NHO		NHO	No NHO	
Period of Intubation (days)	<1	0 (0%)	19 (7%)	>0.999	-	-	-
	2-5	0 (0%)	17 (7%)	>0.999	-	-	-
	6-10	0 (0%)	11 (4%)	>0.999	-	-	-
	11-15	0 (0%)	4 (1%)	>0.999	-	-	-
	16-25	1 (10%)	9 (4%)	0.327	-	-	-
	>25	3 (30%)	7 (3%)	0.004	-	-	-
	Unknown	4 (40%)	57 (23%)	0.245	-	-	-
	Not noted	2 (20%)	128 (51%)	0.103	-	-	-
Spasticity		5 (50%)	9 (4%)	<0.001	10 (63%)	65 (48%)	0.303
Level of intoxication		0 (0%)	18 (7%)	>0.999	-	-	-
Urinary tract infections		3 (30%)	23 (9%)	0.065	13 (81%)	78 (58%)	0.104
Albumin (g/L)		35.1±3.7	36.1±4.5	0.387	33.9±2.8	33.2±4.8	0.549
WCC (10 ⁹ /L)		8.0±3.4	7.8±2.8	0.556	7.9±2.7	8.1±2.8	0.823
DVT/PE		4 (40%)	16 (6%)	0.004	4 (25%)	8 (6%)	0.025
Pressure Ulcers	Pre-pressure areas	-	-	-	0 (0%)	2 (2%)	>0.999
	Heels/malleoli	1 (10%)	4 (2%)	0.178	0 (0%)	6 (4%)	>0.999
	Sacral area/buttocks	0 (0%)	3 (1%)	>0.999	4 (25%)	13 (10%)	0.085
	Ischial tuberosity	-	-	-	1 (6%)	6 (4%)	0.551
	Multiple pressure ulcers	-	-	-	5 (31%)	9 (7%)	0.008
	Miscellaneous (ear)	0 (0%)	1 (1%)	>0.999	-	-	-
Associated Injuries	High risk but not noted	1 (10%)	3 (1%)	0.145	-	-	-
	Nil noted	8 (80%)	241 (95%)	0.082	6 (38%)	99 (73%)	0.007
	Pre-pressure areas	-	-	-	0 (0%)	2 (2%)	>0.999
	Length of stay	143±117	54.7±16.2	<0.001	207±175	122±113	0.055
Smokers/non smokers		1 (10%)	32 (13%)	>0.999	5 (31%)	26 (19%)	0.324
Multiple injuries		6 (60%)	59 (23%)	0.017	2 (13%)	11 (8%)	0.631
Spinal dislocation		-	-	-	13 (81%)	78 (58%)	0.104

Characteristic	TBI			TSCI		
	NHO	No NHO		NHO	No NHO	
Co-morbidities						
Asthma	0 (0%)	5 (2%)	>0.999	0 (0%)	9 (7%)	0.598
Cardiovascular disorders	0 (0%)	7 (3%)	>0.999	0 (0%)	4 (3%)	>0.999
Orthopaedic disorders	1 (10%)	5 (2%)	0.210	1 (6%)	14 (10%)	>0.999
Systemic disorders	1 (10%)	10 (4%)	0.354	1 (6%)	7 (5%)	>0.999
Chronic pain	0 (0%)	2 (1%)	>0.999	0 (0%)	2 (1%)	>0.999
Psychiatric disorders	2 (20%)	17 (7%)	0.158	0 (0%)	3 (2%)	>0.999
Alcoholism	0 (0%)	20 (8%)	>0.999	0 (0%)	3 (2%)	>0.999
Miscellaneous co-morbidities	1 (10%)	8 (3%)	0.299	0 (0%)	14 (10%)	0.364
CCI	0.6±0.9	0.3±0.7	0.175	0.2±0.4	0.5±0.8	0.410

TBI - Traumatic brain injury, TSCI – Traumatic spinal cord injury, NHO – Neurogenic heterotopic ossification, ASIA – American Spinal Injuries Association, ISNCSCI – International Standard for Neurological Classification of Spinal Cord Injury, AIS –ASIA Impairment scale, PTA – Post-traumatic amnesia, GCS- Glasgow coma scale, PE - Pulmonary embolus, DVT – Deep vein thrombosis, CCI – Age-adjusted Charlson Comorbidity Index, WCC – White Cell Count.

Nominal variables are presented as numbers; continuous variables are presented as mean ± standard deviation. Continuous and nominal variables were compared between subjects with and without NHO using Mann Whitney U test and Fisher's exact test, respectively. (Charlson et al., 1987)

Using logistic regression analysis and adjusting for age and gender, DVT/PE remained a common predictor of NHO in both TBI patients (OR=10.35, 95% CI=2.51-43.63, P=0.001) and TSCI patients (OR=5.57, 95% CI=1.41-21.98, P=0.014) (Table 5.6). Spasticity (OR=27.75, 95% CI=6.40-120.27, P<0.001) followed by the period of intubation >25 days (OR=18.73, 95% CI=3.64-96.24, P<0.001), urinary tract infection (OR=6.74, 95% CI=1.55-29.27, P=0.011), and multiple injuries (OR=5.70, 95% CI=1.54-21.07, P=0.009) were identified as predictors of NHO in TBI patients (Table 5.6). Similarly, multiple pressure ulcers (OR=5.61, 95% CI=1.55-20.30, P=0.009) and AIS score B (OR=3.59, 95% CI=1.09-11.79, P=0.035) were predictors of NHO in TSCI patients (Table 5.6).

Table 5.6

Multivariate association of risk factors with NHO in patients with traumatic brain and spinal cord injuries. Reznik et al., 2014)

Risk factor	TBI			TSCI		
	OR	95% CI	P	OR	95% CI	P
DVT/PE	10.35	2.51-43.63	0.001	5.57	1.41-21.98	0.014
Spasticity	27.75	6.40-120.27	<0.001	-	-	-
Period of intubation (>25 days)	18.73	3.64-96.24	<0.001	-	-	-
Urinary tract infections	6.74	1.55-29.27	0.011	-	-	-
Multiple injuries	5.70	1.54-21.07	0.009	-	-	-
Length of stay	1.00	1.00-1.01	0.120	-	-	-
Multiple pressure ulcers	-	-	-	5.61	1.55-20.30	0.009
AIS score B	-	-	-	3.59	1.09-11.79	0.035
AIS score D	-	-	-	0.20	0.02-1.65	0.136

TBI - Traumatic brain injury, TSCI – Traumatic spinal cord injury, DVT – Deep vein thrombosis, AIS –ASIA Impairment scale, PE - Pulmonary embolus, OR, odds ratio; CI, 95% confidence intervals; P, P-value. The association between individual risk factors and NHO was adjusted for age and gender.

5.4 Discussion

In the current study a group of 413 patients with traumatic brain and spinal cord injuries were screened for the presence of NHO. The findings provide evidence that prevalence of NHO in TBI patients is less than one-third of that found in TSCI patients, in particular accounting for ~4% and 11%, respectively. These findings are similar to older estimates of NHO prevalence being about 3% and 4% in TBI and TSCI patients, respectively (Damanski, 1961; Goldman, 1980). More recently published figures however, are at least five-times higher in both neurological conditions (Sakellariou et al., 2012). The prevalence of NHO varies widely among institutions, as some specialised units screen for NHO routinely (Citak et al., 2012) while others report only clinically significant NHO cases (Cipriano, et al., 2009; Teasell, et al., 2010). The relatively conservative estimates of NHO prevalence in TBI and TSCI patients in this study are most likely due to the screening protocol in place at these units, since some of the most prominent complications of NHO, such as joint ankylosis, manifest themselves only in small number of patients (Mavrogenis et al., 2011).

The most notable finding from this study was that the risk factors associated with NHO in TBI and TSCI patients were almost completely distinct, suggesting that clinically significant NHO following traumatic brain and spinal cord injuries are clearly separate entities in terms of their associated risk factors. In addition we found an increase in the number of deep vein thromboses (DVT) prior to the diagnosis of NHO among the TBI and TSCI patients who subsequently developed NHO.

DVT remained the only common risk factor for NHO in these patients even after adjustment for other clinically relevant variables such as age and gender. This is expected as both TBI and TSCI patients often present with a number of additional risk factors associated with DVT development, including major surgery, fractures of the pelvis, hip, or long bones, and trauma, all of which can stimulate the levels of thrombogenic factors, such as factor III or thromboplastin, within the circulation (Martinelli, Bucciarelli, & Mannucci, 2010). Current understanding of the NHO pathogenesis supports the idea that multiple factors are crucial for its initiation and progression rather than a single risk factor such as DVT (Sakellariou et al., 2012). Indeed, approximately half of the TBI and TSCI patients who developed NHO had no symptoms of DVT. In descending order, according to the effect size, TBI patients with

spasticity, period of intubation greater than 25 days, urinary tract infections, and multiple injuries had a higher risk of developing NHO. Most of these risk factors have been previously reported to be associated with NHO (Citak et al., 2012); however, prolonged endotracheal intubation may represent a novel risk factor for NHO in TBI patients. A similar but more invasive surgically based ventilation technique, a tracheostomy, was previously associated with increased risk of NHO in TSCI but not TBI patients (Citak et al., 2012). This was not the case in the TSCI group, where patients with multiple pressure ulcers, and AIS score B had the highest risk of developing NHO. One of the most important orthopaedic concerns for NHO is its ability to impair the mobility of sufferers. In this context, the functional significance of AIS B incomplete lesions as a risk factor for NHO is arguable, since mobility is already severely limited in this group of patients (Kirshblum et al., 2011).

There are many reasons why risk factors for NHO are distinct in TBI and TSCI patients. It is possible that the mode of injury may contribute to the mechanisms of NHO formation, as the causes of upper motor neuron lesions were considerably different in TBI and TSCI patients. The prevalence of assaults and pedestrian motor vehicle accidents was significantly higher in traumatic brain injury cases, whereas sporting, flying, and industrial accidents appeared to be significantly more prevalent in patients with spinal cord injuries. These causes of TSCI frequently lead to prolonged or chronic physical impairments associated with the pressure ulcers (Lyder, 2003), a recognised risk factor for NHO in TSCI patients (Citak et al., 2012). Pressure ulcers also had the highest effect size in this study. On the other hand, assaults to the head often result in an increase in muscle activity and spasticity (Wright, Kellermann, McGuire, Chen, & Popovic et al., 2013); spasticity is a recognized risk factor for NHO in TBI patients (Citak et al., 2012).

NHO is found predominantly in the larger joints such as hips, knees, shoulders, and elbows (Seipal et al., 2012; Simonsen et al., 2007). In the current study we found that NHO predominantly developed in the elbow of TBI rather than TSCI patients. The exact mechanism for this finding is not evident in the current study; however TBI patients significantly differed from those with TSCI in terms of their risk factors for NHO development, including the level of spasticity. Thus it is reasonable to suggest that upper limb spasticity, associated with mechanical stress to the musculotendinous

junction at the elbow joint, might account for the relatively higher number of TBI patients who developed NHO around the elbow. This hypothesis is supported by previous findings that micro trauma may induce ossification through induction of local inflammatory responses or by releasing osteoblast-stimulating factors (Silver, 1969).

Finally, some circulating inflammatory markers such as serum albumin and white blood cell count in TBI and TSCI patients were also assessed. Patients with and without NHO were found to have similar levels of these blood-borne indicators of systemic inflammation. This is in accord with previous findings which provides evidence that the use of common anti-inflammatory agents, such as indomethacin, ibuprofen and aspirin, has only limited effectiveness in the pharmacological management of NHO (Cipriano et al., 2009). Thus other clinical interventions such as extracorporeal shock wave therapy (ESWT) should be investigated for their effectiveness in these patients (Reznik et al., 2013a, 2013b).

The current study has several limitations; in order to minimise some of the difficulties in identifying patients, the study was conducted at specialised brain injury and spinal cord injury units at one rehabilitation centre that implemented the OACIS system. This tool allows for gathering relevant clinical data and patients characteristics in a very uniform, precise manner. As a result of this design, NHO was identified only when it was a clinically significant condition, thus the number of TBI and TSCI patients with NHO was relatively small, which may limit the statistical power, and the number of risk factors identified in the study. This study, moreover, was a retrospective audit, and the findings need to be confirmed in a large prospective study. A further limitation was that the majority of available TBI and TSCI patients were male, limiting the relevance of our findings to NHO in women. Finally, it must be noted that the period of intubation for the TSCI patients was not available using the OACIS tool, and might be useful information to have in future studies.

In conclusion, this study suggests that the risk factors associated with NHO in TBI patients are distinct from those identified in TSCI patients. These findings may have practical implications in the clinical management of patients with NHO following traumatic neurological injuries.

5.5 Key points

- NHO is found predominantly in the larger joints of both TBI and TSCI patients, such as hips, knees, shoulders, and elbows.
- The prevalence of NHO in TBI patients is less than one-third of that found in TSCI patients, ~4% and 11%, respectively.
- The risk factors associated with NHO in TBI patients may be distinct from those identified as risk factors in TSCI patients.
- Risk factors identified from this study:
 - DVT/PE remained a common predictor of NHO in both TBI and TSCI patients,
 - Spasticity followed by the period of intubation >25 days, urinary tract infection and multiple injuries were identified as predictors of NHO in TBI patients, and
 - Multiple pressure ulcers and AIS score B were predictors of NHO in TSCI patients.
- Circulating clinical inflammatory markers were similar in those patients with and without NHO, indicating that treatment with anti-inflammatory agents may not be the most effective treatment for NHO.

Chapter 6. Prevalence of Neurogenic Heterotopic Ossification in Traumatic Head and Spinal Injured Patients admitted to a Tertiary Referral Hospital in Australia

6.1 Introduction

The third guiding question in this thesis, “*what is the prevalence of NHO in TBI and TSCI patients in non-specialised units?*” will be addressed in this chapter. Clinically significant NHO in TSCI patients has been previously determined to be between 10% and 53% (Teasell et al., 2010); in the TBI population the prevalence of NHO has been reported as being between 10% and 20% (Cipriano et al., 2009) (Chapter 5). No comparative epidemiological data of NHO prevalence, however, is available for health-care facilities that are not specialised in treating patients with neurological trauma. In order to address this deficiency of existing data, a retrospective audit over a six and a half year period was carried out at a large tertiary hospital in September 2013. This chapter was published in the Health Care Manager (Reznik et al., 2015)

(Abstract available in Appendix 3D - full paper available on-line at [http://researchonline.jcu.edu.au/31276/.](http://researchonline.jcu.edu.au/31276/))

6.2 Materials and methods

The study was approved by the Human Ethics Committees at The Townsville Hospital (TTH) [HREC/12/QPAH/390; SSA/12/QTHS/227] and James Cook University (JCU), Australia [H4943]; the protocols conformed to the Declaration of Helsinki. TTH is the only tertiary hospital in North Queensland, although not considered to be a specialised unit for TSCI and TBI patients (The Townsville Hospital and Health Service 2012-2013 Annual Report.)

6.2.1 Identification of patients

Patients were identified using the Hospital Based Corporate Information System (HBCIS) and Transition II (TII) tools. At TTH, HBCIS is used to record inpatient and outpatient activity, including revenue and clinical coding. Data relating to emergency department attendances, radiology, pharmacy and pathology are not included in HBCIS. TII is used to record data relating to inpatient activity and clinical coding, costing and

acuity. All data were extracted using Crystal Reports 2008, which is a SAP Business Objects^(c) (Australia) application and were exported to the Microsoft Excel[®] 2003 spreadsheet.

6.2.2 Audit protocol

Retrospective data were provided by the clinical information services of the Townsville Hospital and Health Service. These data comprised all patients with head and/or spinal injuries, and/or heterotopic ossification (HO)/myositis ossificans (MO). Patients aged 18 years or over at the time of admission and who were discharged from TTH between 1 July 2006 and 31 December 2012 were also included. The data were then searched for patients with ICD-10-AM codes indicating traumatic spinal cord injury (TSCI) or traumatic brain injury (TBI), with resultant injury to the nervous system. Demographic data relating to age, length of stay (LOS) and discharge destination were also noted.

Patient diagnoses for TSCI or TBI were further identified using the ICD-10-AM codes for TSCI/TBI (S06, S09, S14, S24, S34, T09) and M61 for HO/MO.

The data were then filtered to identify patients with a length of stay (LOS) < 60days and a LOS $\geq$ 60 days, and not currently recorded on Townsville HBCIS database as being deceased. The selection criterion of 60 days for LOS was chosen as NHO rarely becomes clinically relevant earlier than two months post trauma (Mavrogenis et al., 2011; van Kuijk et al., 2002).

Data were also extracted for any patients aged 18 years or over at the time of admission, with a diagnosis of HO or MO, using the data code M61 for HO/MO and who were discharged from TTH between 1 July 2006 and 31 December 2012.

ICD-10-AM (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification*) refers to the Australian modification of the World Health Organization (WHO) ICD-10 base classification system. This version of ICD has been modified to serve particular Australian needs and to support the national collection of data relevant to the Australian population's health. It is mandatory in all Australian hospitals and is purported to permit and support the systematic recording, analysis, interpretation and comparison of morbidity data. ICD-10-AM is used to translate diseases and other health problems from words into an

alphanumeric code, allowing for easy storage, retrieval and analysis of the data. ICD-10-AM has been regularly reviewed and updated since its first release and implementation in 1998.

Clinical coding is undertaken by trained coders after the discharge of the patient from hospital. Coders apply international standards when coding diseases, injuries and procedures. They review the section of the patient's medical record relating to the inpatient episode of care to determine all of the clinical codes relevant to the patient's admission. Coders rely on the documentation in the patient chart; they can only code the documented diagnoses, and cannot diagnose from results in a chart.

Patients with a date of death were excluded from the data set. Queensland Health does not always receive notification regarding deaths, so not all death-related data can be assumed to be accurate, unless the patient died in hospital. The absence of a date of death in HBCIS does not necessarily mean that the patient is not deceased.

6.2.3 Statistical analysis

Nominal variables are presented as numbers, while continuous variables are presented as mean with ranges in brackets. Nominal and continuous variables were compared using the Fisher's exact test and the Mann-Whitney U test, respectively. Statistical significance was defined at the conventional 5% level. All computations were performed using the StatsDirect version 2.7.9 statistical software (StatsDirect, Ltd

6.3 Results

Using the HBCIS and TII tools, 3172 patients with ICD-10-AM codes for TSCI/TBI were identified between July 2006 and December 2012 (Table 6.1). The mean age of the patients was 43 years (range 18-93 years) and the mean LOS was 14 days (range 1-1054 days; Table 6.1). The majority of TSCI/TBI patients were discharged home from the hospital, only 12% (388/3172) being discharged to another facility. The number of TSCI/TBI patients hospitalized per month increased from 25 in the period 2006-2007 to 64 in the period 2012-2013 (Figure 6.1).

Table 6.1

Number of patients admitted to a tertiary referral hospital between 2006 and 2013 identified by the ICD-10-AM codes for TSCI/TBI .
(Reznik et al., 2015)

Characteristic		Period						Overall	
		2006-2007	2007-2008	2008-2009	2009-2010	2010-2011	2011-2012		2012-2013
Total number of patients		298	370	502	553	515	548	386	3172
Age in years (range)		38 (18-85)	42 (18-86)	41 (18-87)	44 (18-91)	45 (18-92)	45 (18-91)	46 (18-93)	43 (18-93)
Length of stay in days (range)		13 (1-87)	14 (1-263)	15 (1-1054)	14 (1-156)	14 (1-183)	13 (1-905)	15 (1-123)	14 (1-1054)
Discharge destination	Home	182 (61%)	238 (64%)	336 (67%)	347 (63%)	367 (71%)	329 (60%)	259 (67%)	2058 (65%)
	Another facility	54 (18%)	63 (17%)	75 (15%)	67 (12%)	45 (9%)	57 (10%)	27 (7%)	388 (12%)

Age is defined as the chronological age of the patient in years at the date of admission. Period is defined as the time between 1st July and 30th June of the two consecutive calendar years. Period 2012-2013 represents only six calendar months, i.e. from 1st July to 31st December 2012. Nominal variables are presented as numbers, while continuous variables are presented as mean (range).

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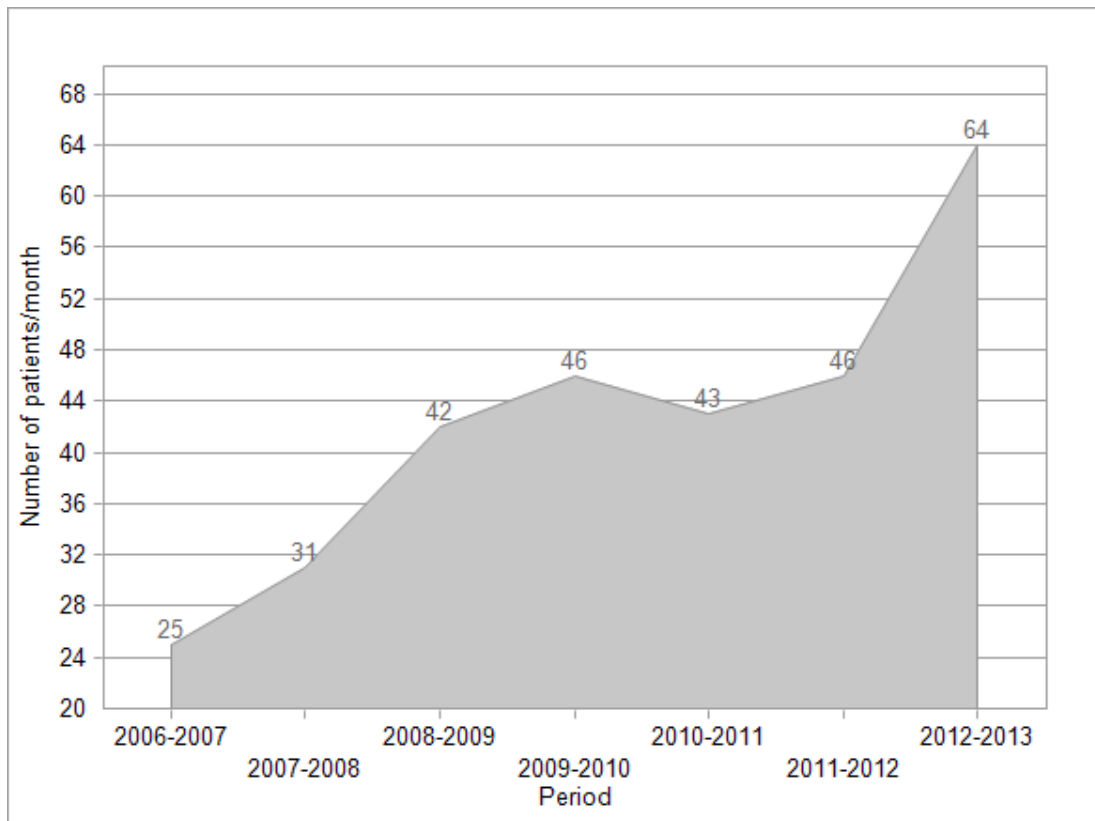


Figure 6.1 Number of TSCI/TBI patients admitted per month to a tertiary referral hospital between 2006 and 2013.

Period is defined as the time between 1st July and 30th June of the two consecutive calendar years. Period 2012-2013 represents only six calendar months, i.e. from 1st July to 31st December 2012 (Reznik et al., 2015)

For those TSCI/TBI patients with a $LOS \geq 60$ days the results show that during the period 2011-2012 a minimum number of five patients with TSCI/TBI was recorded (mean $LOS=257$ days, range=67-905 days; Table 6.2), whilst a maximum number of 13 patients with TSCI/TBI was recorded during the period 2009-2010 (mean $LOS=103$ days, range=68-156 days; Table 6.2). The period 2012-2013 represented only six calendar months i.e. from July 1st to December 31st 2012 with only five long-stay patients with TSCI/TBI being recorded (mean $LOS=92$ days, range=63-123 days; Table 6.2). TSCI/TBI patients with $LOS < 60$ days had similar discharge destinations (discharged home 65% (2020/3114), discharged to another facility 12% (381/3114); (Table 6.3) as compared to TSCI/TBI patients with $LOS \geq 60$ days (discharged home 66% (38/58), discharged to another facility 12% (7/58); (Table 6.2) but were younger (mean age=43 years, range 18-93 years; Table 6.3) compared to TSCI/TBI patients with $LOS \geq 60$ days (mean age=60 years, range 31-87 years; Table 6.2). The difference in age was statistically significant ($P < 0.0001$).

Table 6.2
 Characteristics of patients with TSCI/TBI hospitalised for ≥ 60 days. (Reznik et al., 2015)

Characteristic		Period						Overall	
		2006-2007	2007-2008	2008-2009	2009-2010	2010-2011	2011-2012		2012-2013
Total number of patients		6	7	10	13	12	5	5	58
Patients with TBI		6 (100%)	7 (100%)	10 (100%)	11 (85%)	12 (100%)	4 (80%)	5 (100%)	55 (95%)
Patients with TSCI		0 (0%)	0 (0%)	0 (0%)	2 (15%)	0 (0%)	1 (20%)	0 (0%)	3 (5%)
Age in years (range)		39 (31-49)	60 (36-82)	64 (47-87)	65 (35-82)	61 (37-85)	67 (39-86)	57 (50-72)	60 (31-87)
Length of stay in days (range)		68 (60-87)	139 (80-263)	191 (61-1054)	103 (68-156)	120 (61-183)	257 (67-905)	92 (63-123)	135 (60-1054)
Discharge destination	Home	4 (67%)	5 (71%)	4 (40%)	8 (62%)	9 (75%)	4 (80%)	4 (80%)	38 (66%)
	Another facility	0 (0%)	1 (14%)	3 (30%)	1 (8%)	1 (8%)	1 (20%)	0 (0%)	7 (12%)

Age is defined as the chronological age of the patient in years at the date of admission. Period is defined as the time between 1st July and 30th June of the two consecutive calendar years. Period 2012-2013 represents only six calendar months, i.e. from 1st July to 31st December 2012. Nominal variables are presented as numbers, while continuous variables are presented as mean (range).

Table 6.3
Characteristics of patients with TSCI/TBI hospitalised for <60 days. (Reznik et al., 2015)

Characteristic		Period						Overall	
		2006-2007	2007-2008	2008-2009	2009-2010	2010-2011	2011-2012		2012-2013
Total number of patients		292	363	492	540	503	543	381	3114
Patients with TBI		274 (94%)	316 (87%)	476 (97%)	491 (91%)	488 (97%)	489 (90%)	369 (97%)	2903 (93%)
Patients with TSCI		18 (6%)	47 (13%)	16 (3%)	49 (9%)	15 (3%)	54 (10%)	12 (3%)	211 (7%)
Age in years (range)		38 (18-85)	*42 (18-86)	*41 (18-87)	*43 (18-91)	*44 (18-92)	*44 (18-91)	46 (18-93)	*43 (18-93)
Length of stay in days (range)		11 (1-56)	11 (1-53)	11 (1-57)	12 (1-59)	11 (1-56)	11 (1-58)	14 (1-58)	12 (1-59)
Discharge destination	Home	178 (61%)	233 (64%)	332 (67%)	339 (63%)	358 (71%)	325 (60%)	255 (67%)	2020 (65%)
	Another facility	54 (18%)	62 (17%)	72 (15%)	66 (12%)	44 (9%)	56 (10%)	27 (7%)	381 (12%)

Age is defined as the chronological age of the patient in years at the date of admission. Period is defined as the time between 1st July and 30th June of the two consecutive calendar years. Period 2012-2013 represents only six calendar months, i.e. from 1st July to 31st December 2012. Nominal variables are presented as numbers, while continuous variables are presented as mean (range). Nominal variables such as discharge destinations and continuous variable such as age were compared to those of patients with LOS≥60 days (Table 6.2) using the Fisher's exact test and the Mann-Whitney U test, respectively. Statistically significant differences are marked by the asterisk (*).

In addition, six patients were identified with M61 code (HO/MO) during the period of interest between July 2006 and December 2012. Medical records of those six patients with HO/MO were hand searched and none were associated with TSCI or TBI. Three patients with HO/MO had motor vehicle accidents without TSCI or TBI; one was the case of HO/MO following a burns injury; and two cases of HO/MO were diagnosed in patients with carcinoma of the testes and renal cell carcinoma (Table 6.4).

Table 6.4
Patients with Heterotopic Ossification/Myositis Ossificans. (Reznik et al., 2015)

Patient	Clinical characteristics	Applicable to TSCI/TBI
1	Chronic LBP, old MVA 20 years ago with fracture of pelvis	No
2	MVA with multiple fractures but no TBI or TSCI	No
3	HO following burns	No
4	Minor TBI, testicular Ca possible cause of HO	No
5	MVA with multiple injuries but no TBI or TSCI	No
6	Soft tissue calcification possibly due to renal cell Ca	No

LBP, low back pain; MVA, motor vehicle accident; TBI, traumatic brain injury; TSCI, traumatic spinal cord injury; HO, heterotopic ossification; Ca, cancer.

6.4 Discussion

The prevalence of clinically significant NHO in TSCI patients has been previously determined to be between 10% and 53% (Teasell et al., 2010). In the TBI population the prevalence of NHO has been reported as being between 10% and 20% (Bossche & Vanderstraeten, 2005; Cipriano et al., 2009), although a very recent audit by Reznik et al. (2014) at a specialised unit in Australia, describes lower figures of approximately 4% and 11% for TBI and TSCI patients, respectively (Reznik et al., 2014). Over a six and a half year period more than 3,000 patients with TSCI or TBI were admitted to TTH, the tertiary referral hospital providing health-care services for the North Queensland population, and none were diagnosed with NHO associated with TSCI/TBI. The finding is surprising in regard to the large number of patients identified and the fact that the number of TSCI/TBI patients hospitalised per month in TTH more than

doubled during the audited period between July 2006 and December 2013. There are a number of factors that might contribute to our finding of zero percent of NHO prevalence in TSCI/TBI patients admitted to TTH. NHO is usually diagnosed when it becomes clinically significant, i.e. causes pain, interferes with movement and/or restricts function (Mavrogenis et al., 2011; Reznik et al., 2014; van Kuijk et al., 2002). The TSCI/TBI patients were identified using the ICD-10-AM coding system; however, some important complications of NHO such as pain and decreased mobility are also associated with TSCI/TBI itself, suggesting that NHO might remain overlooked due to these overlaps with the TSCI/TBI as a primary cause of admission. Furthermore, NHO typically becomes apparent at two month post-injury (Mavrogenis et al., 2011; van Kuijk et al., 2002). Only a very small percentage of TTH patients with TSCI/TBI were hospitalised for ≥ 60 days (~2%), suggesting that the vast majority of TSCI/TBI patients at discharge (~98%) were, in fact, below the post-injury time-point of the NHO peak manifestation. The highest incidence of TSCI/TBI has been reported as being in the 15-25 year old age group (Neurotrauma Research Program 2014; Williams, Morris, Schache, & McCrory et al., 2009) however our data showed that TSCI/TBI patients admitted to TTH were approximately twice as old as typical TSCI/TBI patients. NHO has also been reported to be primarily diagnosed within this younger age group (Damanski, 1961; Goldman, 1980; Reznik et al., 2014; Sakellariou et al., 2012; Teasell et al., 2010) and thus the age-related differences in the NHO incidence cannot be excluded as a biasing factor in these results. Finally, our data also show that the majority of TSCI/TBI patients admitted to TTH during the audit period were discharged home, with only a small percentage being discharged to another health-care facility. It is not known if any of these patients were subsequently diagnosed with NHO.

In a recent study undertaken at specialised units, Reznik et al., (2014) suggested deep vein thrombosis to be the only common risk factor in the development of NHO in both the TSCI and TBI populations. Additional risk factors in the TBI population were the length of time the patient was intubated, the level of spasticity and the number of associated injuries. In the TSCI population the additional risk factors included the completeness of the lesion or the presence of multiple pressure ulcers (Reznik et al., 2014), thought to be the major complication of prolonged hospitalisation (Allman, 1997). Since the ICD-10-AM system does not allow for coding of those additional

clinical characteristics, the system may be considered fundamentally ineffective as a registering tool for the severe complications associated with TSCI/TBI such as NHO.

In conclusion, NHO is a relatively common complication of neurological trauma. Taking this fact into consideration, our findings of zero percent of NHO prevalence in a large group of TSCI/TBI patients admitted to the large tertiary referral hospital suggest that NHO may have been missed, possibly due to the TSCI/TBI ICD-10-AM codes not being primarily designed for documentation of the TBI/TSCI complications. Recommendations forthcoming from this study include regular screening for NHO, if the TSCI/TBI ICD-10-AM codes are being recorded, especially in those patients with prolonged hospitalisation. If NHO remains undiagnosed it may later prove to be an extremely debilitating condition in an already functionally compromised individual.

6.5 Key Points

- More than 3000 patients were admitted to a tertiary referral hospital (TTH) diagnosed with TBI/TSCI over a period of six and a half years; none were diagnosed with NHO.
- Six patients identified with HO, did not have an associated TBI/TSCI.
- The ICD-10-AM coding may not allow for the attribution of NHO in the TBI/TSCI patient groups.
- Regular screening for NHO is recommended in these patients groups particularly in patients with prolonged hospitalisation (i.e. ≥ 60 days).

Chapter 7. Extracorporeal Shock Wave Therapy (ESWT) as a Treatment for Recurrent Neurogenic Heterotopic Ossification (NHO)

7.1 Introduction

The fourth guiding question “*how effective is ESWT in the treatment of NHO in TBI patients?*” will be answered in two parts. The first part, a report of a single case study, will be presented in this chapter. This chapter was published in Brain Injury (Reznik et al., 2013a). (Full paper available in Appendix 3E) The second part, an interventional experimental study, is reported in Chapter 8.

This study examines the effect of ESWT in a case of recurrent femoral NHO following traumatic brain injury (TBI).

7.2 Case study

7.2.1 History

GA is a 43 year old female living in Israel. At the time of this intervention she was more than 10 years post severe TBI following a road traffic accident. Her Glasgow Coma Score on admission was 3. She was unconscious for more than three months following her injury. Throughout the time she was unconscious she was treated in intensive care, where she had chest physiotherapy and passive movements daily. Also at this time, one month of inhibitory casting was applied to the right elbow, in an attempt to reverse tightness in her right elbow flexors. Following her slow return to consciousness she was moved from intensive care to a rehabilitation ward where physiotherapy, occupational therapy and speech therapy were provided on a daily basis. At this stage, psychological treatment was also introduced, because GA had sustained a severe diffuse axonal injury and had many behavioural issues and cognitive deficits, as well as physical injuries.

After more than 12 months hospitalisation with intensive rehabilitation, GA was discharged to live in the community with her parents. Her residual impairments included spasticity and weakness on the right side and ataxia on the left side. She had a

mild contracture of the right elbow (5° flexion) and limitation of wrist and finger movements in the right hand due to spasticity and weakness. She was right side dominant. Deep and superficial sensory disturbances were present on the right and left sides of the body. GA walked independently with a walking frame. Her two children lived with their father and his new wife but visited their mother regularly. Over the years there had been substantial improvement in her functional level and abilities and GA now, ten years post injury, was able to live in her own apartment with a 24 hour caregiver.

GA's behavioural disturbances, as well as limited insight, were noted from the earliest days of her return to consciousness, so she required full supervision during most of her daily activities. During the intervening years she continued to receive rehabilitation in the form of physiotherapy, riding therapy, hydrotherapy and art therapy. She continued to suffer from cognitive, behavioural and motor deficiencies. During the last three years, i.e. from seven to ten years post injury, physiotherapy treatment concentrated on strengthening and mobilizing her right upper and lower limbs, improving balance reactions in sitting and standing and improving all gait parameters. Although she had regained much movement in her right upper limb and used it during dual tasks, she still had a preference for using the left hand.

During GA's initial hospitalisation (2001) it was noted that she had a developing NHO around her right hip which resulted in decreased range of motion and pain around the hip joint with consequent loss of function. One year post injury (2002) GA underwent successful surgery for the removal of NHO around the right hip. Post-surgery she resumed physiotherapy and hydrotherapy, with the result that the hip joint movement returned to within normal limits. Pain was between 1 and 2 on the Visual Analogue Scale (VAS).

GA maintained good functional mobility of the right hip over the next six years, but in 2008, (eight years post injury) she began again to complain of pain around the right hip joint and severe movement limitation was noted (Table 7.1).

Table 7.1
Results: Pre- and Post -Treatment. (Reznik et al., 2013a)

	Pre-treatment date	Post-treatment date								
	3.1.10	6.1.10	13.1.10	27.1.10	3.02.10	24.2.10	24.3.10	24.4.10	25.5.10	24.10.10
Flexion (°), Hip (R)	85	90	100	100	90	100	95	95	90	90
Internal Rotation (°), Hip (R)	20	30	30	40	35	30	25	30	30	30
External Rotation (°), Hip (R)	30	35	40	45	45	45	35	40	45	35
Adduction (°), Hip (R)	10	10	10	20	15	15	20	20	20	10
Abduction (°), Hip (R)	30	30	30	40	30	35	35	35	35	30
Extension (°), Hip (R)	0	0	0	0	0	-5	-5	-5	-5	0
Pain (VAS)	9/10	9/10	0/10	0/10	0/10	0/10	0/10	0/10	2/10	0/10
Number of steps over 28 metres	87	83	82	71	70	75	75	78	80	75

Plain x-rays and MRI revealed that NHO had recurred (Plate 7.1).



Plate 7.1 NHO around the right hip joint as indicated by arrows on plain X-ray (Pre-treatment). (Reznik et al., 2013a)

Due to the number of complications that may arise following surgery (Melamed et al., 2002), GA's treating orthopaedic surgeon did not consider her to be a suitable candidate for further surgical intervention. Pharmacological intervention was also not considered since it was well known that GA was not compliant in taking medication. As a result of the increased pain, GA became unwilling to walk long distances and her low psychological tolerance levels were causing frequent violent outbursts as observed by her treating physiotherapist and reported by her caregivers. Since the pain was reducing her functional level to that of a non-walker, the non-invasive treatment option of ESWT, as described in the literature by Brissot et al. (2005), was considered to be a reasonable treatment option. With the approval of GA, her legal guardians (parents) and her treating orthopaedic surgeon, a decision was made to apply a novel treatment approach with ESWT.

7.2.2 Outcome measures

Outcome measures included:

- Goniometric measurements of all right hip movements with the patient in supine
- The level of pain experienced assessed using the visual analogue scale (VAS)
- The number of steps required to cover a distance of 28 metres (the length of the driveway from GA's car to the physiotherapy clinic)

All measurements were taken immediately prior to the administration of ESWT and at weekly intervals throughout the six week intervention (Table 7.1). Plain radiographs of the hip joint were taken prior to treatment and post treatment. GA's walking pattern and social behaviours were observed but not formally assessed.

7.3 Methods

A Minispec™ Extracorporeal Shock Wave machine (Medispec Int. USA) was used to deliver four applications of ESWT over a six week period to the area of the right hip joint corresponding to the underlying position of the NHO. Treatments were given by YA (the treating orthopaedic registrar) at the Department of Orthopaedics, Assaf Harofe Hospital. Three thousand shock waves were delivered at each treatment to the anterior aspect of the right hip at the intensity level of 5-6. During the period that GA was receiving the ESWT, all other treatments, including physiotherapy, hydrotherapy, riding therapy and psychology, continued as usual.

7.4 Results

Following four treatments of ESWT to the right hip, GA gained range of movement in all planes in the right hip and a longer step length on the right, as demonstrated by a reduced number of steps over a set distance (Figure 7.1). The longer right step length appeared to lead to improved symmetry in GA's walking pattern compared to her pre-treatment walking pattern. Pain was reduced from 9 to 0 on the VAS following the first application of ESWT (Figure 7.1). As a result of these improvements, GA was able to walk more efficiently, at a faster speed, for a greater distance and with more stability (Figure 7.1).

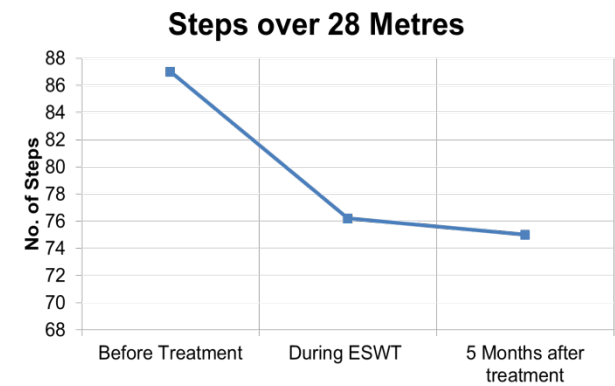
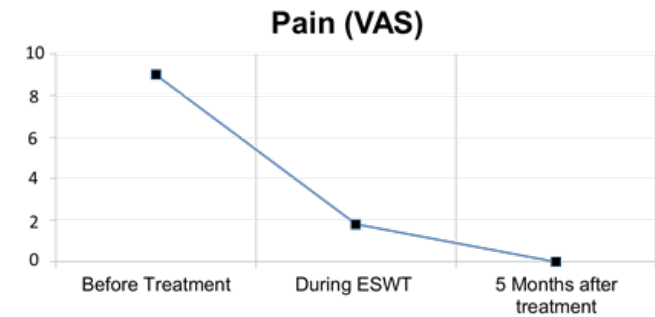
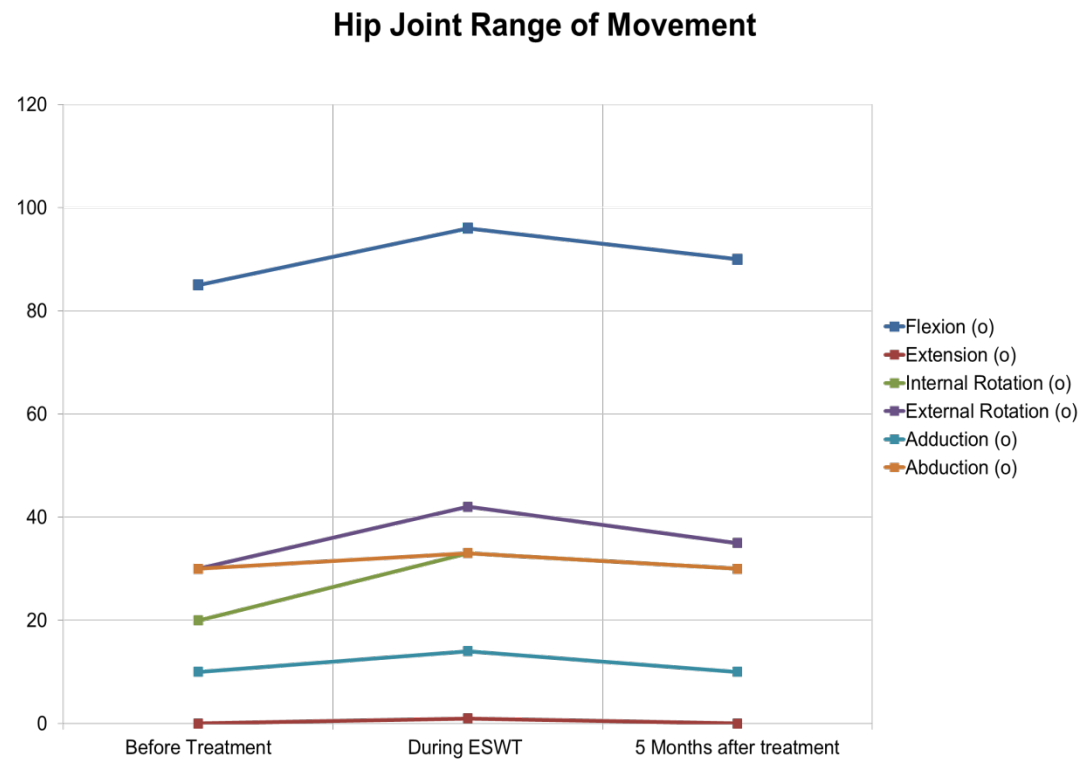


Figure 7.1 Graphs of ROM, VAS and no. of steps over 28 metres.
 ROM, Range of motion; VAS, visual analogue scale

Comparison of X-rays taken pre- and post-treatment showed no major radiographic changes (Plate 7.2).

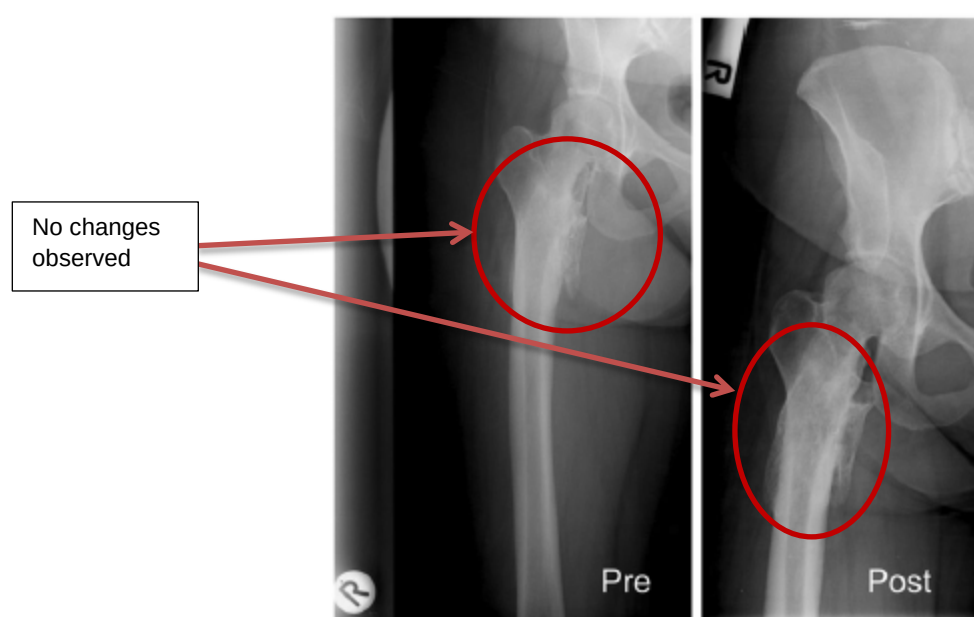


Plate 7.2 X-ray of right hip pre and post-treatment. (Reznik et al., 2013a)

Five months after treatment, during which time GA had minimal therapy intervention, movements at GA's right hip were re-measured. She had retained the gains she had previously made, there was no recurrence of pain and her step length continued to increase. The changes in range of movement, pain and function over time are reported in Table 7.1 and Figure 7.1.

Anecdotally, her carers reported an improvement in social behaviours and a decrease in her violent outbursts.

7.5 Discussion

The initial gains made by GA in ROM and the reduction of pain were maintained for at least five months post treatment and as a consequence function improved in the form of better-quality gait. The only known, definitive, currently available treatment for NHO is surgical excision. This is a major procedure with numerous associated complications and post-operative recurrence is common (Melamed et al., 2002). Identification of a non-surgical (invasive) treatment method would, therefore, be valuable in this patient group.

As there were no radiological changes following the four treatment sessions with extracorporeal shock waves, it is possible that the immediate improvement in GA's ROM and function were related to pain reduction and/or microscopic changes in the ossification and/or fibrotic changes. Wang, in his studies on treatments for osteonecrosis of the hip in 2005 and 2008, also found that there were significant improvements in pain and function of the hip without changes on MRI (C-J. Wang et al., 2005, 2008). Since ESWT has been shown to effectively reduce pain (Helbig, Herbert, Schostok, Brown, & Thiele et al. 2001; Rompe et al., 1996) and reduction in pain can positively affect behavioural and cognitive responses (Sator- Katzenschlager et al., 2003), it is possible that GA's behavioural responses became more manageable due to a reduction in her pain, this in turn leading to an improvement in function.

If the actual size of the mass of bone had not been reduced, what then caused the reduction in pain and allowed an increased range of motion? Since anti-inflammatory medication has been shown to have a positive effect on the signs and symptoms of NHO (Banovac, 2000; Banovac et al., 1997; Garland et al, 1983; Stover et al., 1976), it is possible that the ESWT may exert an anti-inflammatory effect on NHO, which might explain the reduction in pain observed in our case study. In future studies bone scans would be useful in assessing this effect.

Maier et al. (2003) reported an increase in the release of substance P within the first 24 hours after application of shock wave therapy, and a decrease six weeks later. This time course closely approximates that of the clinical time course of an initial increase in pain followed by a later reduction after application of shock wave therapy. Although Haake et al. (2002) showed no effect of EWST on the spinal nociceptive system, a later study in rats showed that ESWT reduces the expression of calcitonin gene-related peptide (CGRP), a marker of sensory neurons involved in pain perception in dorsal root ganglia (Takahashi et al., 2003). ESWT applied to the rat footpad caused degeneration and re-innervation of sensory nerve fibres innervating the skin (Ohtori et al., 2001). Murata et al. (2006) showed that EWST induced injury of sensory fibres, followed by rapid regeneration. Although both small and large diameter fibres were damaged, a greater proportion of large-diameter fibres were affected. Activity in large-diameter axons modulates nociceptive signals transmitted by small-diameter axons in the dorsal horn (Basbaum & Fields, 1978). Rompe et al. (1996) suggested that the intense input of the

shockwaves activates the small diameter fibres which project to cells in the periaqueductal grey area. This in turn may activate a descending serotonergic system which ultimately modulates transmission through the dorsal horn (Melzack, 1975, 1994; Rompe et al., 1996). Moreover, subsequent applications of EWST have a cumulative effect on sensory fibres, thus providing a longer-lasting effect on pain (Takahashi et al., 2006). Wess (2008) has suggested that EWST may disrupt the neural circuitry giving rise to chronic pain, and thereby lead to pain relief.

In addition to its anti-nociceptive effect, EWST induces new blood vessels in the region of application, with angiogenic markers being expressed within a week, and vascularisation commencing four weeks post-treatment and continuing for 12 weeks (Wang et al., 2003). While angiogenesis promotes healing and pain relief in conditions such as chronic tennis elbow (Rompe et al., 1996) or non-union of long bone fracture (Schaden, Fischer, & Sailer 2001) the effect of angiogenesis in the case of NHO is yet to be elucidated.

ESWT has been effective in reducing both acute and chronic pain in a variety of orthopaedic pathologies (Helbig et al., 2001; Ogden et al., 2001; Rompe, Hope, Kullmer, Heine, & Burger, 1996; Rompe, Rosendahl, Schollner, & Theis, 2001; Schaden et al., 2001). Buselli et al. (2010), in a recent paper on the treatment of myositis ossificans with ESWT in sportsmen, concluded that it is the reduction of pain which leads to an increase in function. These findings are supported by our study. Since spasticity was not evaluated quantitatively it is not possible to discern if the effect of ESWT was directly on the pain and/or through reduction of spasticity around the treated joint.

This report actually raises more questions than answers:

1. Why was there a small, yet noteworthy, increase in the range of motion around the hip joint, without reduction of bone mass?
2. What was the mechanism underlying the reduced pain post-ESWT?
3. What was the effect post-ESWT that allowed the gains to last for a long time without any further intervention?

The very promising results presented here warrant further investigation with a larger sample of spinal cord and brain injured patients who have developed NHO.

7.6 Key points

- Following four treatments with high energy ESWT there was an immediate reduction of pain, an increase in the ROM of the hip and an increase in step length.
- These results were maintained for at least 5 months.
- This case study suggests that ESWT may be a non-invasive, low risk intervention for the management of NHO.

Chapter 8. Series of Single Case Research Studies: Efficacy of Extracorporeal Shock Wave Therapy (ESWT) for Neurogenic Heterotopic Ossification (NHO) in the hip or knee of a patient following Traumatic Brain Injury (TBI)

8.1 Introduction

This chapter discusses the second part of the question ““how effective is ESWT in the treatment of NHO in TBI patients?” This clinical trial will be submitted as a paper when all the results have been collated.

As discussed in Chapter 2, treatments to date for neurogenic heterotopic ossification (NHO) have been pharmacological, surgical, or a combination of the two. Non-steroidal anti-inflammatory drugs (NSAIDs) have the greatest efficacy in the prevention of NHO when administered early after injury, and bisphosphonates have demonstrated the highest efficacy in both SCI and TBI patients in reducing the development of NHO (Aubut, et al., 2011; Teasell, et al., 2010). The pharmacological treatments, however, have not proven to be successful once NHO has formed. On the basis of a single randomised controlled trial (RCT), there is evidence supporting the efficacy of pulsed low-intensity electromagnetic field (PLIMF) therapy in prophylaxis of NHO after SCI (Durovic, et al., 2009). Surgical removal has been advocated by some authors (Melamed, et al., 2002) but is extremely invasive and not always possible for this group of patients.

Despite the extensive use of extracorporeal shock wave therapy (ESWT) in the treatment of a range of musculoskeletal conditions, (Chapter 3), NHO following TBI or TSCI has received only a limited attention (Brissot et al., 2005; Buselli et al., 2010; Reznik et al., 2013a; Torrance & deGraauw, 2011). Treatment of the musculoskeletal system using ESWT has been found to have virtually no serious side-effects (Haake, et al., 2002; Speed, 2004).

8.1.1 Research Question

Is ESWT effective in reducing pain and improving function in people with TBI who have NHO at the hip or knee joint?

8.1.2 Rationale for Current Study

A single case study using therapeutic ESWT to treat a TBI patient with recurrent NHO at the hip-joint was conducted by Reznik, et al., (2013a) (Chapter 7). The patient showed signs of functional improvement immediately after therapy; she had markedly improved gait, decreased pain and there was an increase in range of motion at the hip-joint. These beneficial effects of ESWT were maintained for at least five months following treatment. The ESWT was administered by an orthopaedic registrar who followed the manufacturer's guidelines for dosage and frequency (Chapter 7).

8.1.3 Study objectives

The primary objective for this study was to investigate whether ESWT was effective in reducing pain and improving physical function in TBI patients with neurogenic heterotopic ossification (NHO). The secondary objective was to investigate whether ESWT has effects on NHO itself, such as a reduction in the size or density of NHO, as measured by plain X-ray.

8.2 Methods

Ethics approval for this study was granted by the Human Research Ethics Committees of Beit Loewenstein Rehabilitation Centre, Israel and James Cook University Townsville, Australia, Research ID: 0020-13-LOE. The study was also registered at ClinicalTrials.gov Identifier NCT02331628.

8.2.1 Study design

The study design was an interventional, experimental study. A series of single case research studies was undertaken where participants were assessed on multiple occasions; i.e. pre-, during, and post-intervention. This design was chosen because NHO is a relatively rare condition and recruitment of an adequate number of participants for a formal RCT would have proven extremely difficult. To avoid the

heterogeneity of patients associated with previous trials, a homogenous group of post – TBI patients with NHO at the hip or knee were recruited.

Participants recruited to the study were TBI patients diagnosed with chronic NHO present for more than one year and who had a stable serum alkaline phosphatase (SAP) level indicating that there was no active ossification process ongoing. Four baseline assessments were conducted at two weekly intervals followed by four interventions of ESWT, again at two weekly intervals. Subsequent to the intervention period four further two weekly follow-up assessments were carried out. Final assessments were made three months and six months post intervention (Table 8.1).

This study took place at Beit Lowenstein Hospital, Ra'anana, Israel between October 13th 2014 and September 13th 2015. An extension of the ethics approval was sought and granted in order to continue recruiting and complete all measures on those participants who were recruited late in this study. (Ethics approval granted until September 13th 2016)

Table 8.1
Study design diagram depicting outcome measures collected during this study.

Baseline				Intervention				Follow-up					
0/52	2/52	4/52	6/52	8/52	10/52	12/52	14/52	16/52	18/52	20/52	22/52	26/52	38/52
VAS	VAS	VAS	VAS	VAS	VAS	VAS	VAS	VAS	VAS	VAS	VAS	VAS	VAS
ROM	ROM	ROM	ROM	ROM	ROM	ROM	ROM	ROM	ROM	ROM	ROM	ROM	ROM
FR/ MFR	FR/ MFR	FR/ MFR	FR/ MFR	FR/ MFR	FR/ MFR	FR/ MFR	FR/ MFR	FR/ MFR	FR/ MFR	FR/ MFR	FR/ MFR	FR/ MFR	FR/ MFR
Gait								Gait				Gait	Gait
FIM				FIM				FIM				FIM	FIM
EQ-5D								EQ-5D				EQ-5D	EQ-5D
SAP level					SAP level						SAP level		
X-ray													X-ray

VAS, Visual Analogue Scale in the form of the Numerical Rating Scale (NRS); Gait, Spatio-temporal gait measures;
ROM, Range of motion in degrees; FR, Functional Reach; MFR, Modified Functional Reach;
FIM, Functional Independence Measure; EQ-5D, European Quality of Life 5–Dimensions questionnaire; SAP, serum alkaline *phosphatase*.

8.2.2 Participants

Eleven patients with traumatic brain injury (TBI) who met the selection criteria were identified from the database of the Beit Loewenstein Rehabilitation Centre, Israel.

8.2.2.1 *Inclusion criteria:*

- Aged over 18
- Traumatic brain injury
- Diagnosed with NHO around the hip or knee for a period of more than one year
- Stable serum alkaline phosphatase (SAP) level at the time of recruitment

8.2.2.2 *Exclusion criteria:*

- Pregnancy
- Suffering from rheumatoid arthritis, ankylosing spondylitis or femoral/pelvic fractures at the time of recruitment

8.2.3 Participant enrolment and recruitment

Participants were contacted by telephone and /or letter and invited to take part in the trial. All participants were asked to attend the Beit Loewenstein Rehabilitation Centre and assessed for their eligibility by the attending Medical Officer and co-investigator (YS).

All participants who met the inclusion criteria were asked to sign the consent form. In those cases where the participants had legal guardians and/or were unable to sign, the legal guardian provided informed consent.

8.2.4 Primary and secondary outcome measures

The primary outcome measures were:

- Self-reported pain using a visual analogue scale (VAS) in the format of the Faces Rating Scale

- Range of motion (ROM) as measured by a universal goniometer
- Functional reach (in sitting or standing) as measured by the Functional Reach Test (FRT) or Modified Functional Reach Test (MFRT)
- Changes in the area of NHO calculated from plain X-rays taken at baseline and at least six months post-intervention. An X-ray view was set up for each patient and recorded so that it could be repeated. The view was not necessarily a standard view; each individual patient had their own particular view which was reproducible. Due to the time frame of this study not all post-intervention X-ray data will be included in the thesis. They will however be analysed and included in the final paper. All measurements were made along co-ordinates - set up for each patient – e.g. the largest and shortest diameters. Qualitative changes and changes in the size of NHO were analysed by an expert radiologist (AL) using the Clearcanvas PACS system (*Clearcanvas Inc. 1920-439 University Avenue, Toronto ON M5G 1Y8*).

Full details of methodology of radiographic analysis can be seen in Appendix 1F.

Secondary outcome measures included:

- The Functional Independence Measure (FIM) assessed at two monthly intervals
- Spatio-temporal gait measures using the 10 metre walk and the 6 minute walk, for those patients who were ambulant, taken pre- and post-intervention and then at three and six months post intervention
- Quality of life, assessed using the EQ-5D-European Quality of Life 5–Dimensions questionnaire pre- and post-intervention, and then at three and six months post intervention.
- Serum alkaline phosphatase levels were taken at weeks 0, 10 and 22, to ensure that the NHO remained inactive.

All physical and qualitative measures were taken by an independent assessor (OK). Full details of these assessments can be seen in Appendix 1E.

8.2.5 Intervention

Using the Minispec TM ESWT machine (Medispec Int. USA) (Plate 8.1) (Appendix 5) all participants received four applications of EWST delivered to the affected hip and /or knee over a period of eight weeks (one dose every two weeks $\pm$ 3 days). All treatments were administered by the principal investigator (JER) under the supervision of the Medical Officer (Plate 8.2). The dosage was calculated from the size of the NHO as seen on X-ray and the area to be treated was marked into one cm² zones (Plate 8.3). The number of shocks per zone was dependent upon the number of zones to be treated but did not exceed 500. The patients received a maximum of 3000 shocks/treatment, with an energy flux density (EFD) per shock of 0.176 mJ/mm². This dosage is considered as high energy EWST according to the Kassel classification (High EFD>0.12mJ/mm²) (Siebert, 2003).

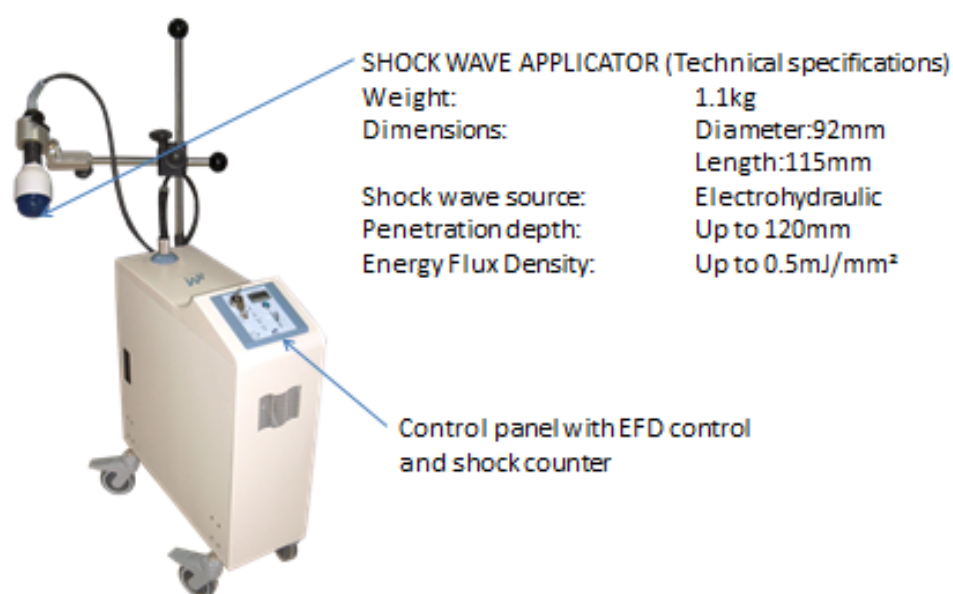


Plate 8.1 Minispec TM System.



Plate 8.2 Application of shockwaves using coupling medium.



Plate 8.3 X Ray and markings over area to be treated.

A water-based gel coupling medium was applied to the membrane and the patient skin area to be treated. (Plate 8.2)

8.2.6 Data Management

A Case Report Form (CRF) (Appendix 4) was used for all data collection. Numerical data were entered directly. De-identified data were entered into an Excel[®] spread sheet and checked for data errors and inconsistencies. The computer was password-secured and accessible only to the chief investigator. The data recorded for this study included basic demographic characteristics, characteristics of the illness, medications and outcome measures. The data were “cleaned” before analysis, checked for data entry errors and general data inconsistencies.

All data were treated with confidentiality in accordance with policies of the treating institution. All members of the research team were bound by similar rules of confidentiality.

8.2.7 Statistical analysis

Visual analogue scale of pain (VAS), range of motion (ROM), Functional reach (FR) and Modified Functional Reach (MFR) data were plotted graphically for visual inspection of trends within baseline, intervention and post-intervention phases. The effect size estimates associated with the application of ESWT were calculated using the non-parametric non-overlap Tau-U method (Parker et al., 2011). The resulting effect size estimates were interpreted as the magnitude of intervention effect in percentages. In particular, the Tau-U score represents the percentage of non-overlap between phases or the percentage of data showing improvement between phases (Parker et al., 2011). Higher Tau-U scores represent greater intervention effect while lower Tau-U scores represent an intervention that is less effective. The Tau-U method is designed to control for baseline trend and is the preferred method to estimate effect sizes when a positive linear trend in therapeutic direction exists in baseline (Parker et al., 2011). All Tau-U score computations were performed using the Tau-U Calculator (Single Case Research™, USA). Statistical significance was defined at the conventional 5% level. Gait, Functional Independence Measure (FIM)², European Quality of Life 5–Dimensions (EQ-5D),³ serum alkaline phosphatase (SAP) level and X-ray data were presented as percent change (D%) D% was calculated using a formula: $D\% = 100 * (\text{intervention or post-intervention value} - \text{baseline value}) / \text{baseline value}$.

8.2.8 Reporting Adverse Events

Participants were asked at each assessment if they had any adverse events to report. All events were documented and reported to the treating MO (YS).

8.3 Results

One participant (Case #4) completed the four baseline measures and the four interventions and measures and was then lost to follow-up. He did however complete the required blood tests allowing measurement of the SAP levels to be documented.

² Assessment chart available in Appendix 1C

³ Assessment chart available in Appendix 1D

8.3.1 Medications

Four out of the 11 participants were not taking any medications. Five out of the seven participants were taking anti-epileptic or anti-convulsant medications; two participants were also taking anti-depressants; three other participants on medications were taking stimulating drugs; two participants were taking medications for spasticity; two participants were taking medications for intractable pain; one participant was taking an anti-psychotic drug, and one participant was also taking medication due to severe insomnia. (Table 8.2)

Medications not related to the participants' TBI i.e. drugs for gastro-intestinal reflux, urinary problems and/ or vitamins were not commented upon.

Table 8.2
Medications.

Patient	Medications (Generic names)
1	None
2	Lamotrigine, Sertaline, Methylphenidate, Amitriptyline
3	None
4	Levetiracetam, Methylphenidate
5	None
6	Methylphenidate, Carbamazepine
7	Pregabalin, Duloxetine, Dopical, Valproic acid, Carbamazepine
8	None
9	Trihexyphenidyl, Brotizolam, Levomepromazine, Risperidone, Oxycodone/ Naloxone, Metamizole
10	Diazepam, Baclofen, Duloxetine
11	Clonazepam, Topiramate

Throughout this study, which continued for 38 weeks, no participant increased or added any medication. The two participants who were taking medications for neuropathic pain reduced or ceased taking these particular medications.

8.3.2 Adverse effects

One participant (Case #7) suffered a fall at home just prior to commencement of the trial. He sustained a fracture of the “not to be treated” hip which was internally fixated

and the decision was made by the MO that since this was a single case research series he could continue at a later date to participate in the trial. One other participant (Case #8) reported a fall in the afternoon following treatment and suggested it might be connected to the treatment. This was documented and the participant examined by the MO. Following full assessment by the MO it was decided that there were no physiological adverse effects related to the ESWT and the reporting was indeed part of the residual behavioural changes following the TBI. Three interventions had been given; it was decided to discontinue any further interventions but the participant agreed to continue with post intervention assessments.

8.3.3 Patient characteristics

The effect of ESWT on chronic neurogenic heterotopic ossification (NHO) was assessed in 11 patients with TBI; four TBI patients presented with NHO in the affected knee and seven TBI patients presented with NHO in the affected hip (Table 8.3). Six patients out of the 11 patients were ambulant (with or without an aid). TBI patients were less likely to be females (18%; 2/11), were of relatively young age (mean age=41±14 years), and had BMI of 25±4 kg/m². NHO tended to occur equally at both sides; 5 out of 11 patients had their right affected side treated and 6 out of 11 TBI patients were treated on their left side (Table 8.3). 7 out of 11 patients had NHO around the hip-joint and 4/11 had NHO around the knee joint. All participants presented with varying degrees of functional and mobility dysfunction (FIM motor score range=56±23; Table 8.3).

Table 8.3
Characteristics of patients included in this study.

Case	Gender	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m ²)	Affected side	Affected joint	Walkers	FIM motor score at baseline
1	m	53	85	171	29	left	hip	yes	79
2	m	52	85	175	28	right	knee	yes with cane	66
3	m	21	60	167	21	left	knee	yes with 4-pt. cane	83
4	m	57	78	174	26	left	knee	yes	75
5	m	26	68	168	24	left	hip	no	56
6	m	62	95	173	32	right	hip	yes	86
7	m	47	74	194	20	right	hip	no	51
8	f	23	58	171	20	right	hip	yes with crutches	73
9	m	35	75	185	22	right	hip	no	25
10	f	44	63	166	23	left	hip	no	13
11	m	36	85	189	29	left	knee	no	37
Overall	-	41±14	75±12	176±9	25±4	-	-	-	56±23

m, male; f, female; A; Overall, mean ± standard deviation (SD);

FIM, functional independence measure. FIM motor scores range from 13 (total dependence) to 91 (total independence) (Appendix 1C)

8.3.4 Effect of ESWT on Pain (VAS)

Pain intensity was assessed using the Faces Rating Scale format of the Visual Analogue Scale for Pain (VAS Pain; Appendix 1E). Nine out of eleven TBI patients completed the intervention phase and the post-intervention phase. Based on the visual assessment of individual distributions of VAS Pain scores during the intervention phase, ESWT was associated with a reduction or no change in VAS Pain scores in most TBI patients compared to their respective baseline phase (Figure 8.1). An increase in VAS Pain scores during the intervention phase compared to the baseline phase was observed only in one patient (Figure 8.1). The significant reduction of VAS Pain scores during the post-intervention phase compared to the respective baseline phase was observed in one patient (Tau=-0.917, 90% CI=-1.560<>-0.274, P=0.019; Table 8.4). The reduction of VAS Pain scores during the post-intervention phase compared to the respective baseline phase was observed in another seven patients, though the difference did not reach statistical significance ($P \geq 0.05$; Table 8.4). Overall Tau score shows that ESWT was associated with significant reduction of VAS Pain score in TBI patients during the post-intervention phase compared to the baseline phase (Tau=-0.424, 90% CI -0.672<>-0.176, P=0.005; Table 8.4).

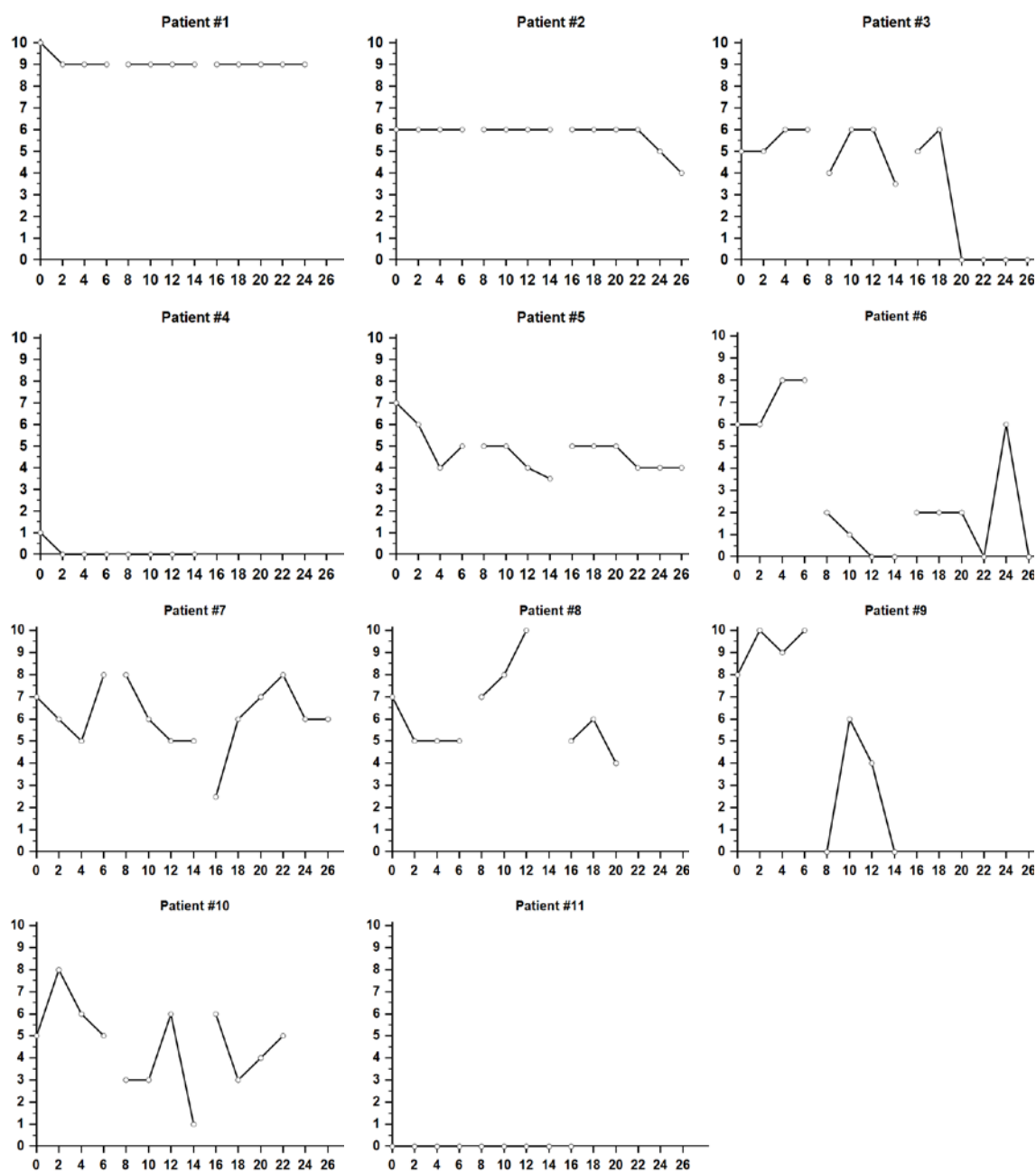


Figure 8.1 Effect of ESWT on Pain (VAS).

Pain intensity was recorded after the application of ESWT during the intervention phase. Horizontal axes, time in weeks; Week 0 to 6, baseline phase; Week 8 to 14, intervention phase; Week 16 to 24, post-intervention phase; Vertical axes, VAS Pain scores. (Patient#11 VAS score 0 throughout)

Table 8.4
Overall effect of ESWT on Pain (VAS).

Patient	Baseline vs Intervention			Baseline vs Post-intervention		
	Tau	CI 90%	P	Tau	CI 90%	P
1	-0.250	-0.962<>0.462	0.564	-0.250	-0.922<>0.422	0.540
2	0.000	-0.712<>0.712	1.000	-0.333	-0.976<>0.310	0.394
3	-0.250	-0.962<>0.462	0.564	-0.667	-1.310<>-0.024	0.088
4	-0.250	-0.962<>0.462	0.564	Lost to follow-up		
5	-0.563	-1.275<>0.150	0.194	-0.500	-1.143<>0.143	0.201
6	-1.000	-1.712<>-0.288	0.021	-0.917	-1.560<>-0.274	0.019
7	-0.250	-0.962<>0.462	0.564	-0.125	-0.768<>0.518	0.749
8	0.917	0.141<>1.692	0.052	-0.250	-1.025<>0.525	0.596
9	-1.000	-1.712<>-0.288	0.021	Not completed		
10	-0.688	-1.400<>0.025	0.112	-0.563	-1.275<>0.150	0.194
11	0.000	-0.712<>0.712	1.000	0.000	-1.163<>1.163	1.000
Overall	-0.312	-0.529<>-0.096	0.018	-0.424	-0.672<>-0.176	0.005

Pain intensity was recorded after the application of ESWT during the intervention phase.

Tau, Tau scores; CI 90%, 90% confidence interval; P, P-value

8.3.4.1 Effect of ESWT on Functional Reach (FR) and Modified Functional Reach (MFR)

Functional Reach (FR) is a clinically accessible measure of balance in standing (Duncan, Weiner, Chandler, & Studenski, 1990) and Modified Functional Reach (MFR) is a measure of sitting balance for those individuals unable to stand (Katz-Leurer, Fisher, Neeb, Schwartz, & Carmeli, (2009).

All six walking patients completed the FR test during the intervention phase and five of those six TBI patients also completed the FR test at the post-intervention phase (Table 8.5). One of the participants, who had no voluntary movements (Case #10) was unable to perform either the FR or the MFR. The visual assessment of individual FR test

results during the intervention phase indicates that ESWT was associated with improved FR test in four out of six patients as compared to their respective baseline phase (Figure 8.2). The positive effect of ESWT on FT results was also clearly seen in two patients at post-intervention phase relative to the respective baseline phase (Figure 8.2). Overall Tau score shows that ESWT was associated with significant improvement in FR test results in walking TBI patients during the intervention phase (Tau=0.421, 90% CI 0.126<>0.717, P=0.019) and the post-intervention phase (Tau=0.502, 90% CI 0.2050<>0.7981, P=0.005) compared to the baseline phase (Table 8.5).

The visual assessment of the MFR test was not conclusive (Figure 8.3). The TBI patients, who were unable to walk, did not present with any statistically significant change in their MFR test results during the both intervention and post-intervention phase compared to the baseline phase (P=0.157 and P=0.839, respectively; Table 8.6).

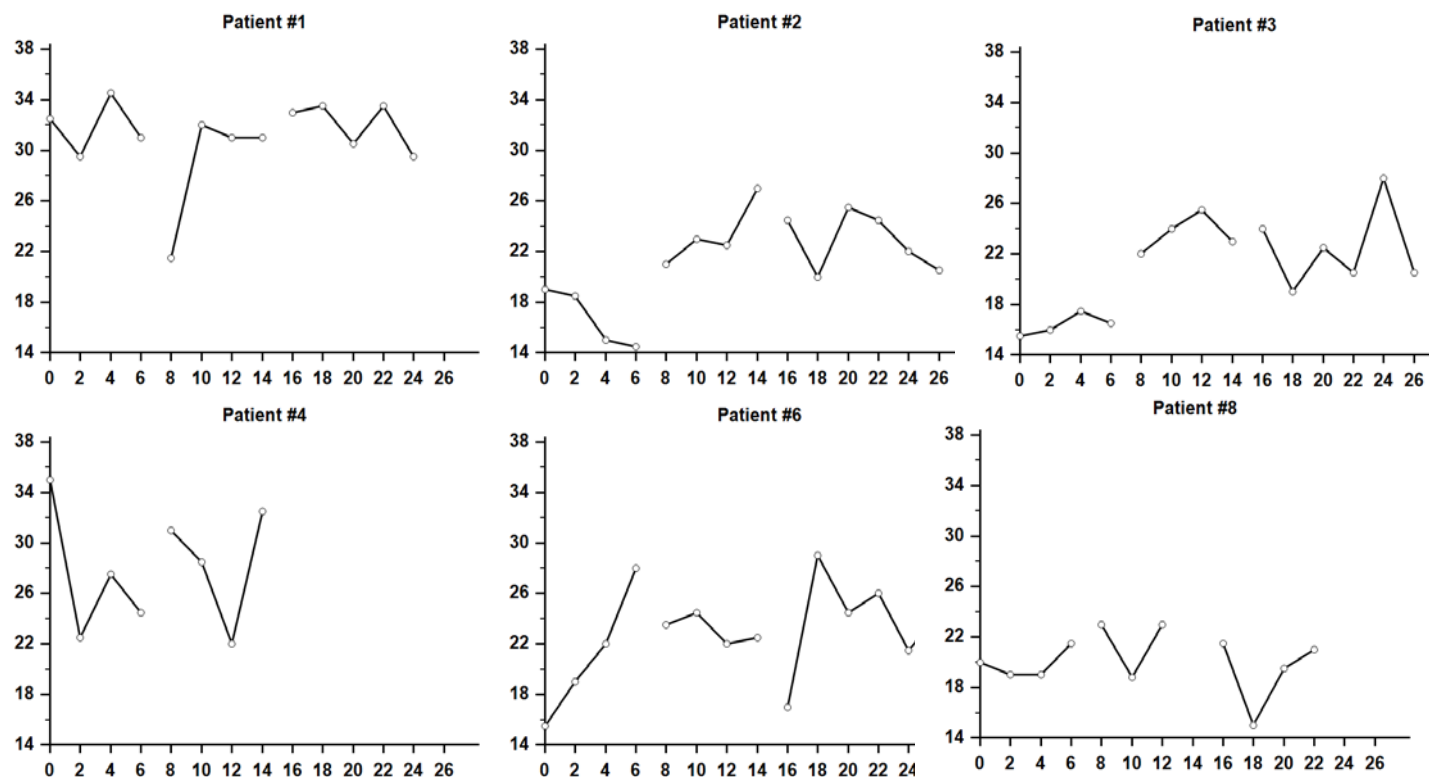


Figure 8.2 Effect of ESWT on Functional Reach.

Horizontal axes, time in weeks; Week 0 to 6, baseline phase; Week 8 to 14, intervention phase; Week 16 to 24, post-intervention phase; Vertical axes, distance in cm as measured by FRT in standing.

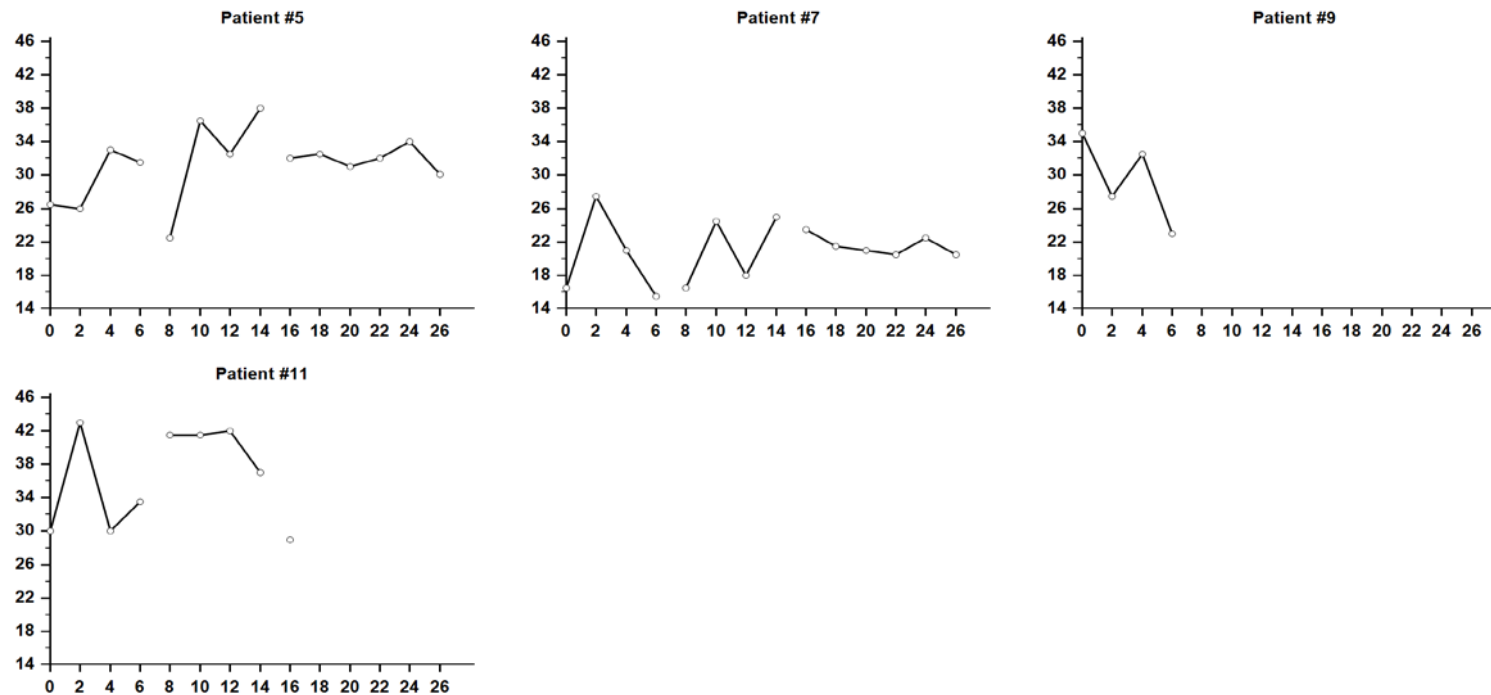


Figure 8.3 Effect of ESWT on Modified Functional Reach.

Horizontal axes, time in weeks; Week 0 to 6, baseline phase; Week 8 to 14, intervention phase; Week 16 to 24, post-intervention phase; Vertical axes, distance in cm as measured by MFRT in sitting.

Table 8.5
Overall effect of ESWT on Functional Reach.

Patient	Baseline vs Intervention			Baseline vs Post-intervention		
	Tau	CI 90%	P	Tau	CI 90%	P
1	-0.375	-1.087<>0.337	0.387	0.050	-0.622<>0.722	0.903
2	1.000	0.663<>2.087	0.002	1.000	0.607<>1.893	0.001
3	1.000	0.288<>1.712	0.021	1.000	0.357<>1.643	0.011
4	0.125	-0.587<>0.837	0.773	Lost to follow-up		
6	0.063	-0.650<>0.775	0.885	0.083	-0.56<>0.726	0.831
8	0.333	-0.442<>1.109	0.480	0.063	-0.65<>0.775	0.885
Overall	0.421	0.126<>0.717	0.019	0.502	0.2050<>0.7981	0.005

Tau, Tau scores; CI 90%, 90% confidence interval; P, P-value.

Table 8.6
Overall effect of ESWT on Modified Functional Reach.

Patient	Baseline vs Intervention			Baseline vs Post-intervention		
	Tau	CI 90%	P	Tau	CI 90%	P
5	0.375	-0.337<>1.087	0.387	0.417	-0.226<>1.060	0.286
7	0.188	-0.525<>0.900	0.665	0.292	-0.351<>0.935	0.456
11	0.500	-0.212<>1.212	0.248	-1.000	-2.163<>0.163	0.157
Overall	0.354	-0.057<>0.765	0.157	0.061	-0.431<>0.553	0.839

Tau, Tau scores; CI 90%, 90% confidence interval; P, P-value.

8.3.5 Effect of ESWT on Knee Range of Motion (ROM)

In order to investigate the effect of ESWT on knee ROM, the two movement parameters (flexion and extension) of the knee were assessed. All four of the recruited TBI patients with NHO around the knee completed the intervention phase and two of those four patients also completed the post-intervention phase. Based on the visual assessment of individual knee flexion data during the intervention phase, ESWT was associated with improved knee flexion in two out of four patients assessed compared to their respective baseline phase (Figure 8.4). The visual assessment of the knee extension data is not informative (Figure 8.5). Overall Tau score shows that ESWT was associated with significantly improved flexion of the knee during the post-intervention phase (Tau=0.859, 90% CI 0.367<>1.351, P=0.004 but not during the intervention phase (Tau=0.094, 90% CI -0.262<>0.450, P=0.665; Table 8.7) compared to the baseline phase. There was no statistically significant effect associated with the application of ESWT on knee extension during the post-intervention phase compared to the baseline phase (Tau=0.114, 90% CI -0.378<>0.606, P=0.703; Table 8.8).

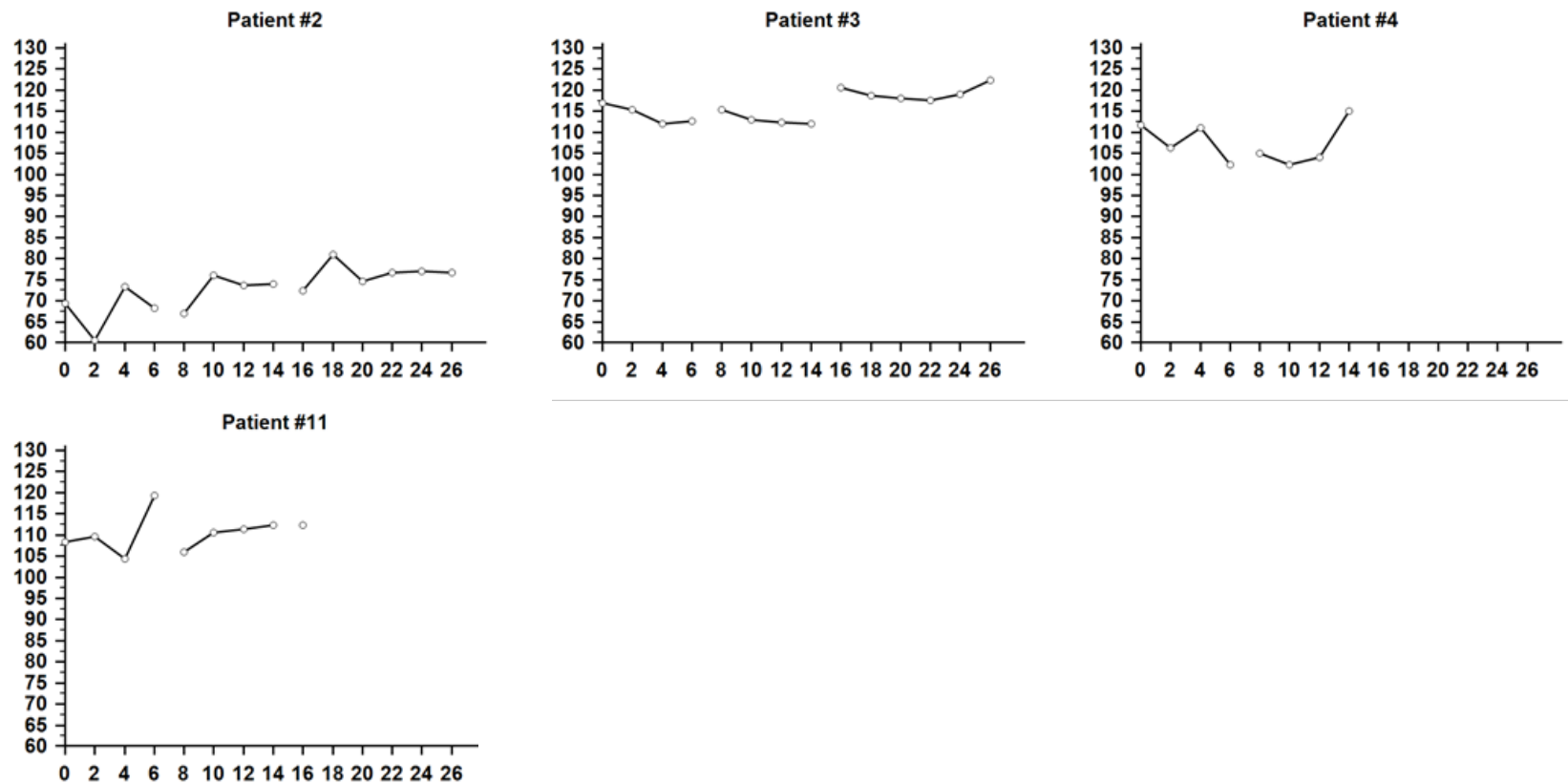


Figure 8.4 Effect of ESWT on Knee Flexion.

Horizontal axes, time in weeks; Week 0 to 6, baseline phase; Week 8 to 14, intervention phase; Week 16 to 24, post-intervention phase; Vertical axes, angle in degrees measured by a universal goniometer.

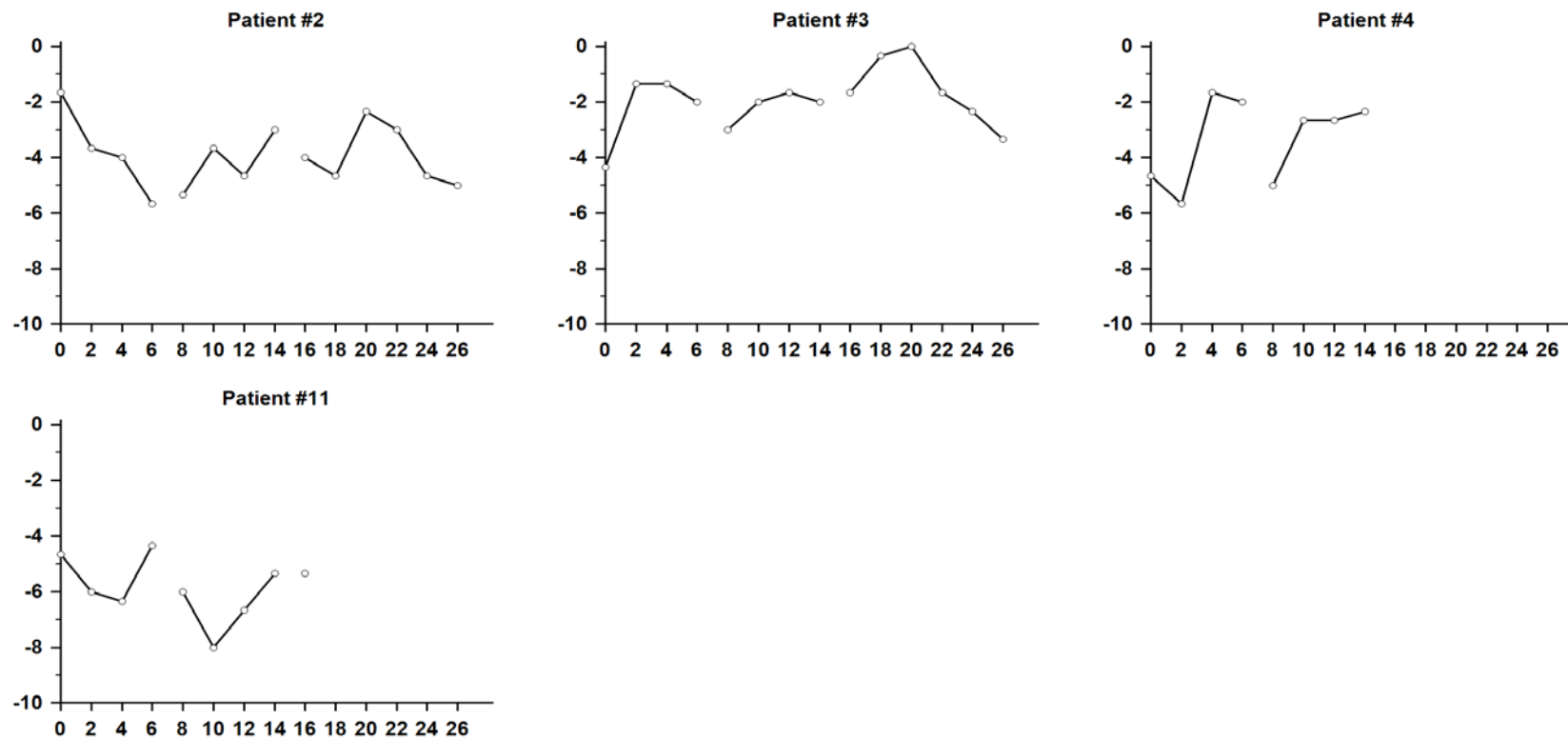


Figure 8.5 Effect of ESWT on Knee Extension.

Horizontal axes, time in weeks; Week 0 to 6, baseline phase; Week 8 to 14, intervention phase; Week 16 to 24, post-intervention phase; Vertical axes, angle in degrees measured by a universal goniometer.

Table 8.7
Overall effect of ESWT on Knee Flexion.

Patient	Baseline vs Intervention			Baseline vs Post-intervention		
	Tau	CI 90%	P	Tau	CI 90%	P
2	0.625	-0.087<>1.337	0.149	0.917	0.274<>1.560	0.019
3	-0.250	-0.962<>0.462	0.564	1.000	0.357<>1.643	0.011
4	-0.250	-0.962<>0.462	0.564	Lost to follow-up		
11	0.250	-0.462<>0.962	0.564	0.500	-0.663<>1.663	0.480
Overall	0.094	-0.262<>0.450	0.665	0.859	0.367<>1.351	0.004

Tau, Tau scores; CI 90%, 90% confidence interval; P, P-value

Table 8.8
Overall effect of ESWT on Knee Extension.

Patient	Baseline vs Intervention			Baseline vs Post-intervention		
	Tau	CI 90%	P	Tau	CI 90%	P
2	0.313	-0.400<>1.025	0.471	0.125	-0.518<>0.768	0.749
3	-0.250	-0.962<>0.462	0.564	0.167	-0.476<>0.810	0.670
4	-0.125	-0.837<>0.587	0.773	Lost to follow-up		
11	-0.563	-1.275<>0.150	0.194	0.000	-1.163<>1.163	1.000
Overall	-0.156	-0.512<>0.200	0.471	0.114	-0.378<>0.606	0.703

Tau, Tau scores; CI 90%, 90% confidence interval; P, P-value

8.3.6 Effect of ESWT on Hip Range of Motion (ROM)

In order to investigate the effect of ESWT on hip ROM, the movement parameters of flexion, extension, abduction, adduction, and internal and external rotation of the hip were assessed. Six out of seven recruited TBI patients with NHO at the hip joint completed the intervention phase and post-intervention phase. Based on the visual assessment of individual hip movement data during the both intervention and post-intervention phase, the application of ESWT was associated with an improved flexion

(Figure 8.6) and extension (Figure 8.7) of the hip compared to their respective baseline phase in some (flexion, n=4 and extension, n=4) but not all TBI patients. The visual assessment of abduction was not informative (Figure 8.8 and 8.9). On the other hand, there was found to be a decreasing trend in hip internal and external rotation during the intervention and the post-intervention phase compared to the respective baseline phase (Figure 8.8 and 8.9, respectively). Overall Tau scores suggest a positive trend in effects of ESWT during the post-intervention phase compared to the baseline phase on flexion (Table 8.9), extension (Table 8.10), abduction (Table 8.11), and adduction (Table 8.12) of the hip, although the effect sizes did not reach statistical significance ($P \geq 0.05$). The application of ESWT was also associated with decreased internal rotation of the hip during the post-intervention phase compared to the baseline phase, though the effect size did not reach statistical significance (Tau=-0.299, CI 90% -0.573<>-0.024, P=0.073; Table 8.13). ESWT was, however, associated with significant decrease in external rotation of the hip during the post-intervention phase compared to the baseline phase (Tau=-0.399, CI 90% -0.673<>-0.125, P=0.017; Table 8.14).

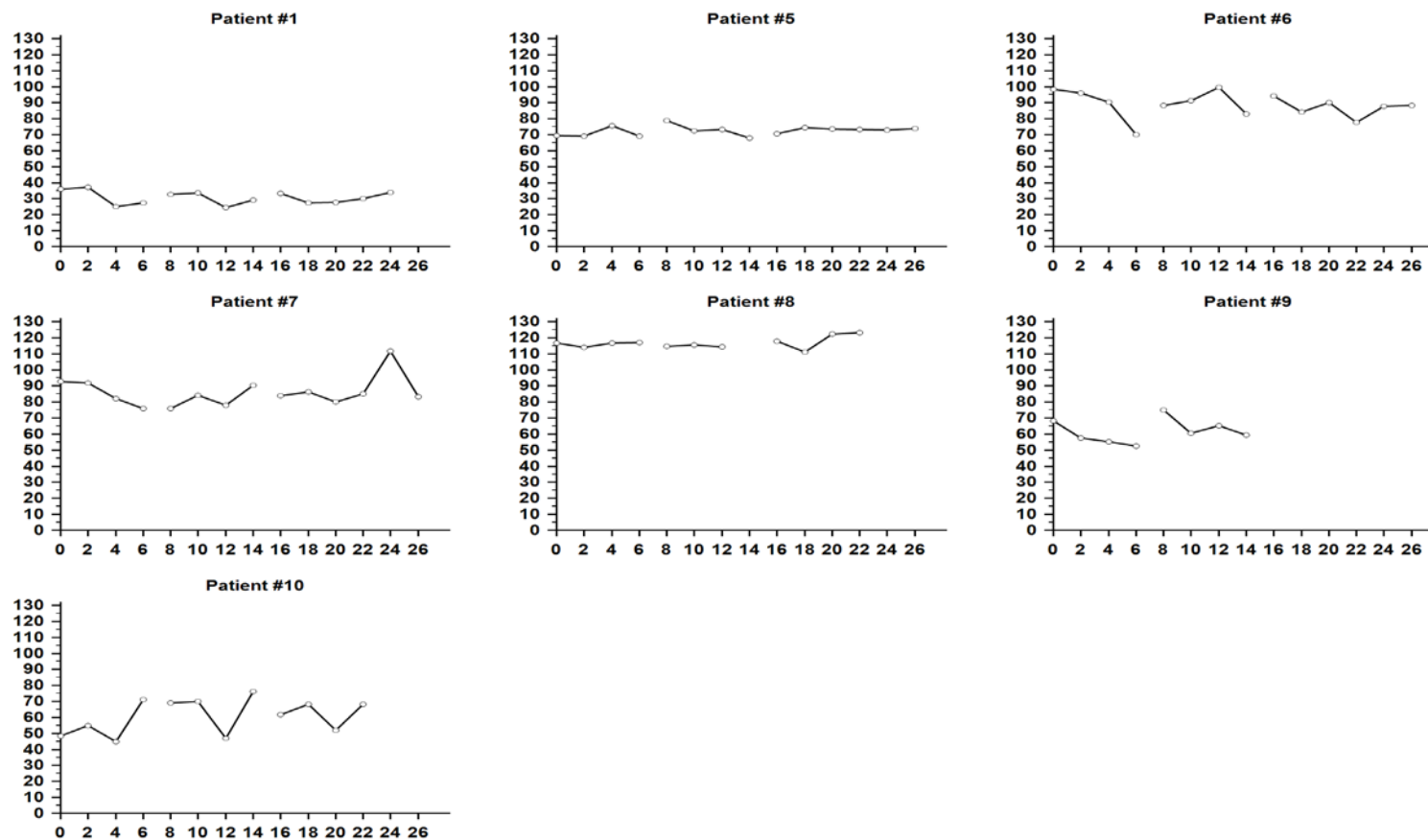


Figure 8.6 Effect of ESWT on Hip Flexion.

Horizontal axes, time in weeks; Week 0 to 6, baseline phase; Week 8 to 14, intervention phase; Week 16 to 24, post-intervention phase; Vertical axes, angle in degrees as measured by a universal goniometer.

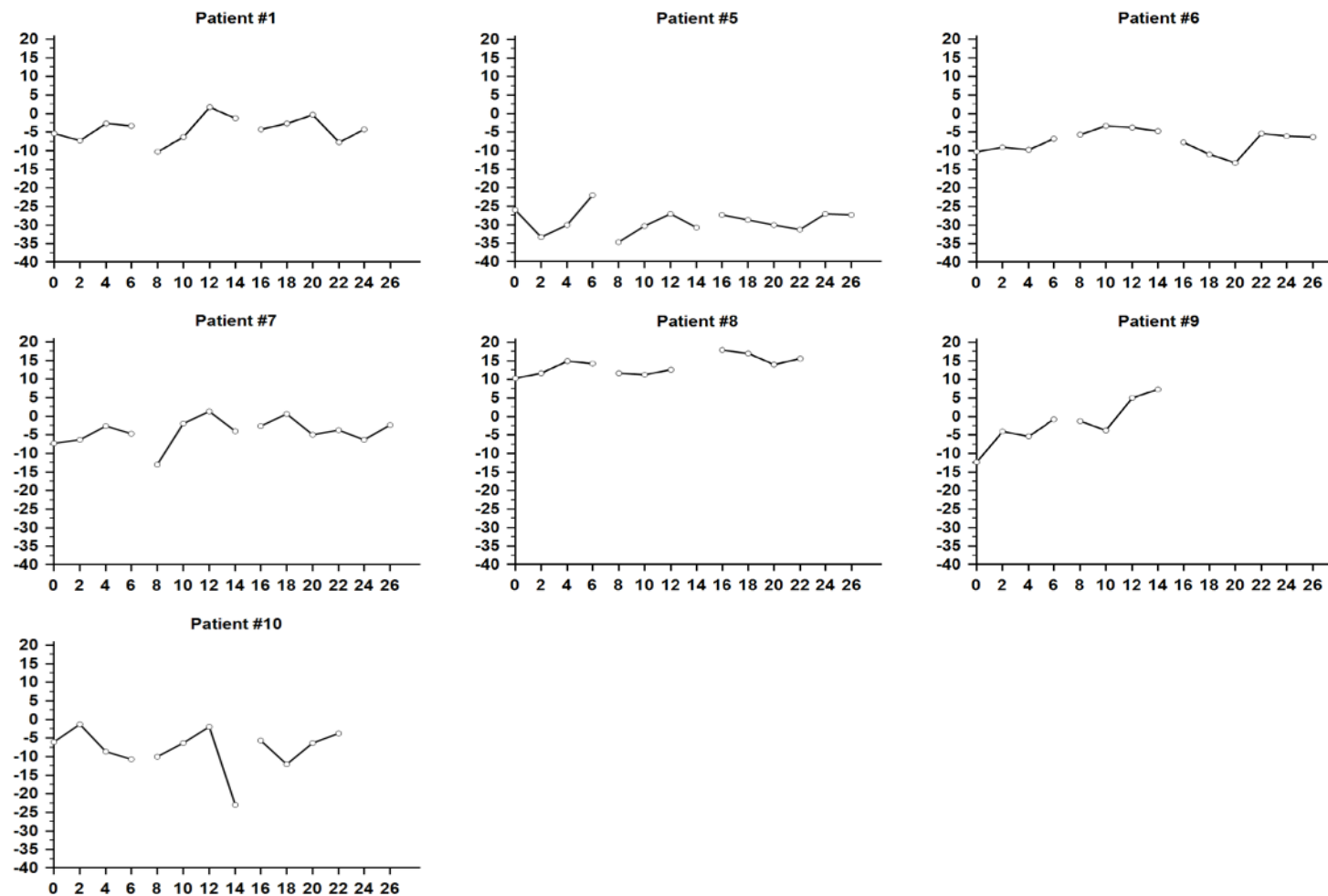


Figure 8.7 Effect of ESWT on Hip Extension.

Horizontal axes, time in weeks; Week 0 to 6, baseline phase; Week 8 to 14, intervention phase; Week 16 to 24, post-intervention phase; Vertical axes, angle in degrees as measured by a universal goniometer.

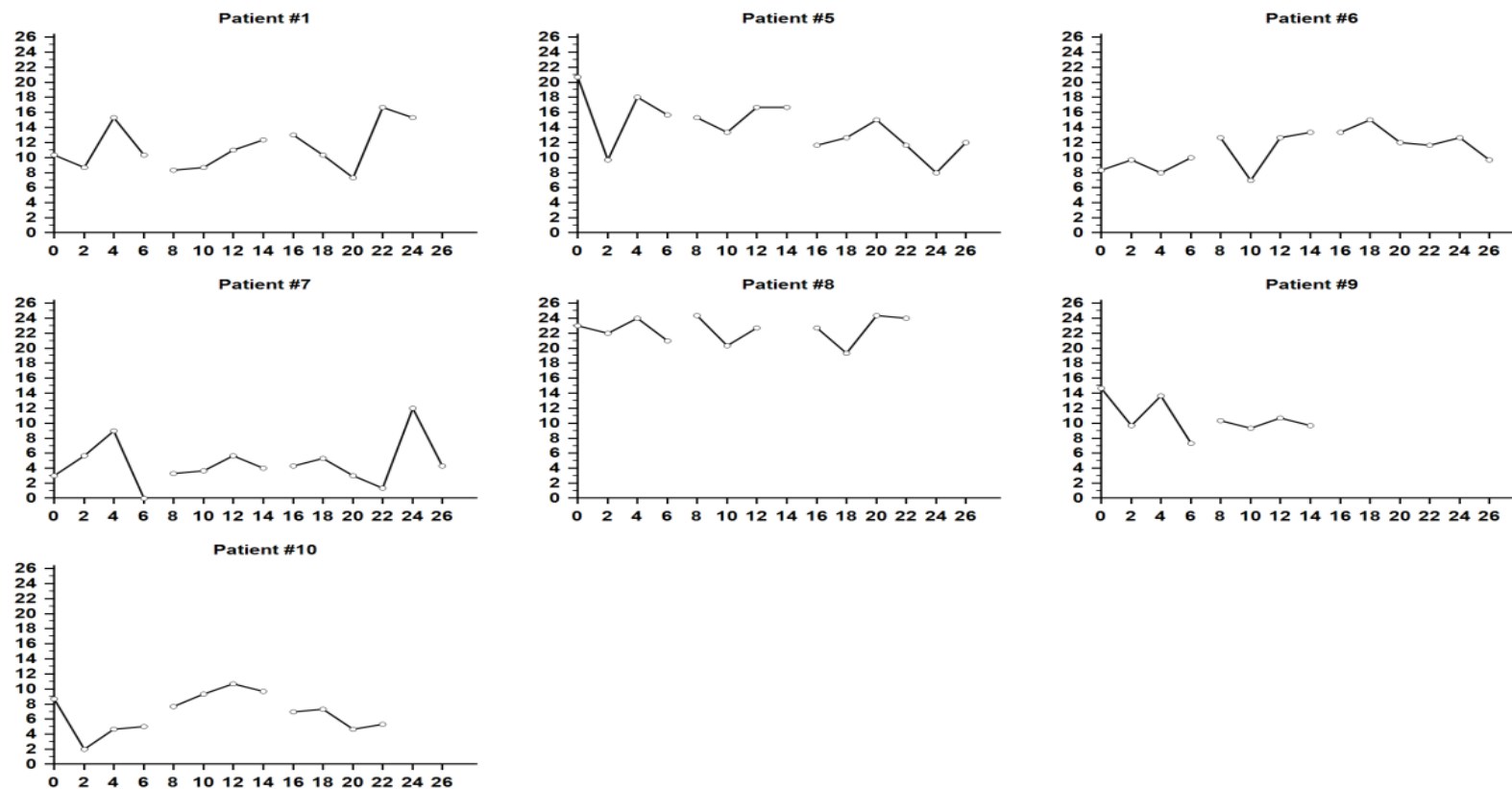


Figure 8.8 Effect of ESWT on Hip Abduction.

Horizontal axes, time in weeks; Week 0 to 6, baseline phase; Week 8 to 14, intervention phase; Week 16 to 24, post-intervention phase; Vertical axes, angle in degrees as measured by a universal goniometer.

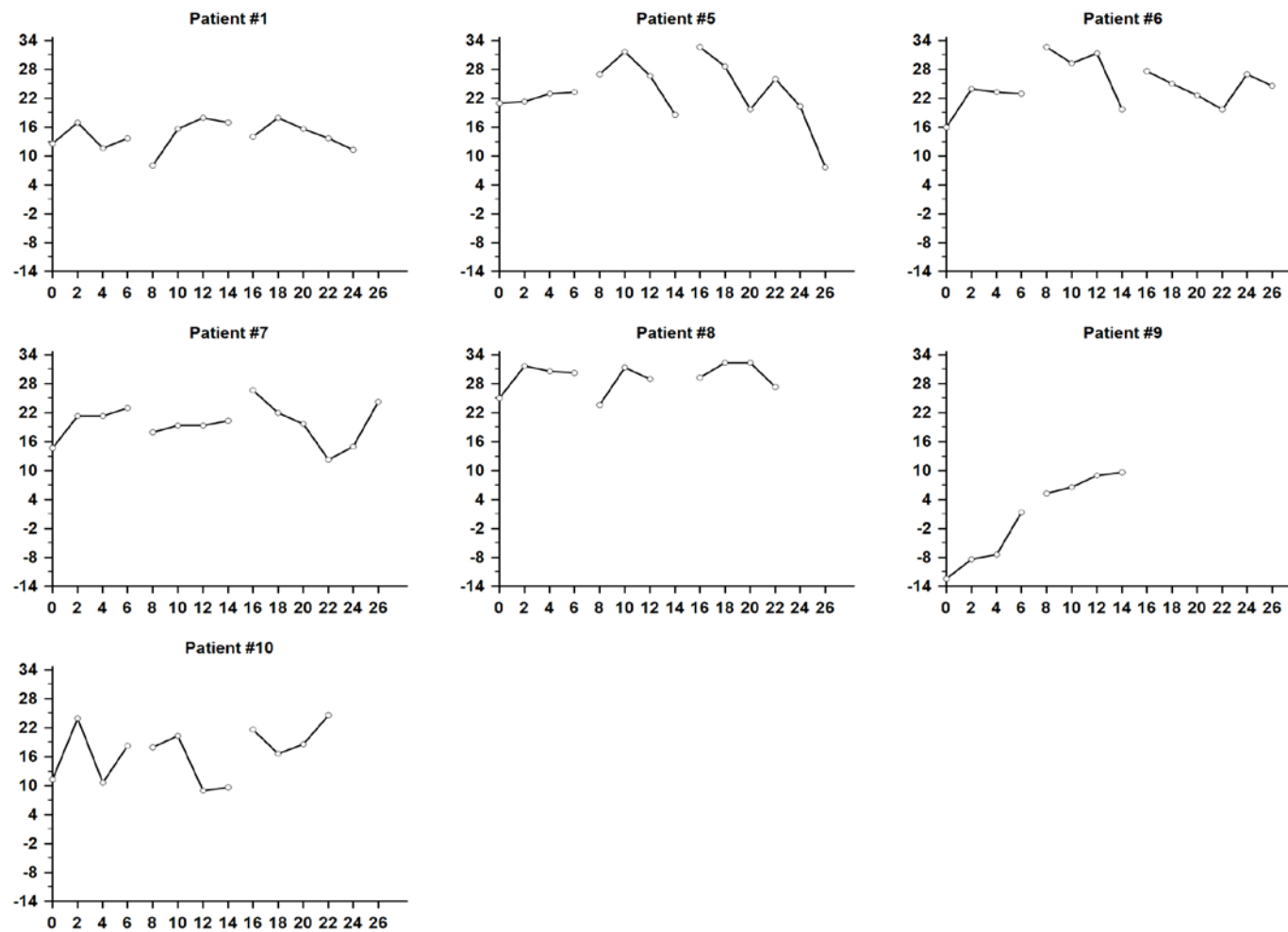


Figure 8.9 Effect of ESWT on Hip Adduction.

Horizontal axes, time in weeks; Week 0 to 6, baseline phase; Week 8 to 14, intervention phase; Week 16 to 24, post-intervention phase; Vertical axes, angle in degrees measured by a universal goniometer

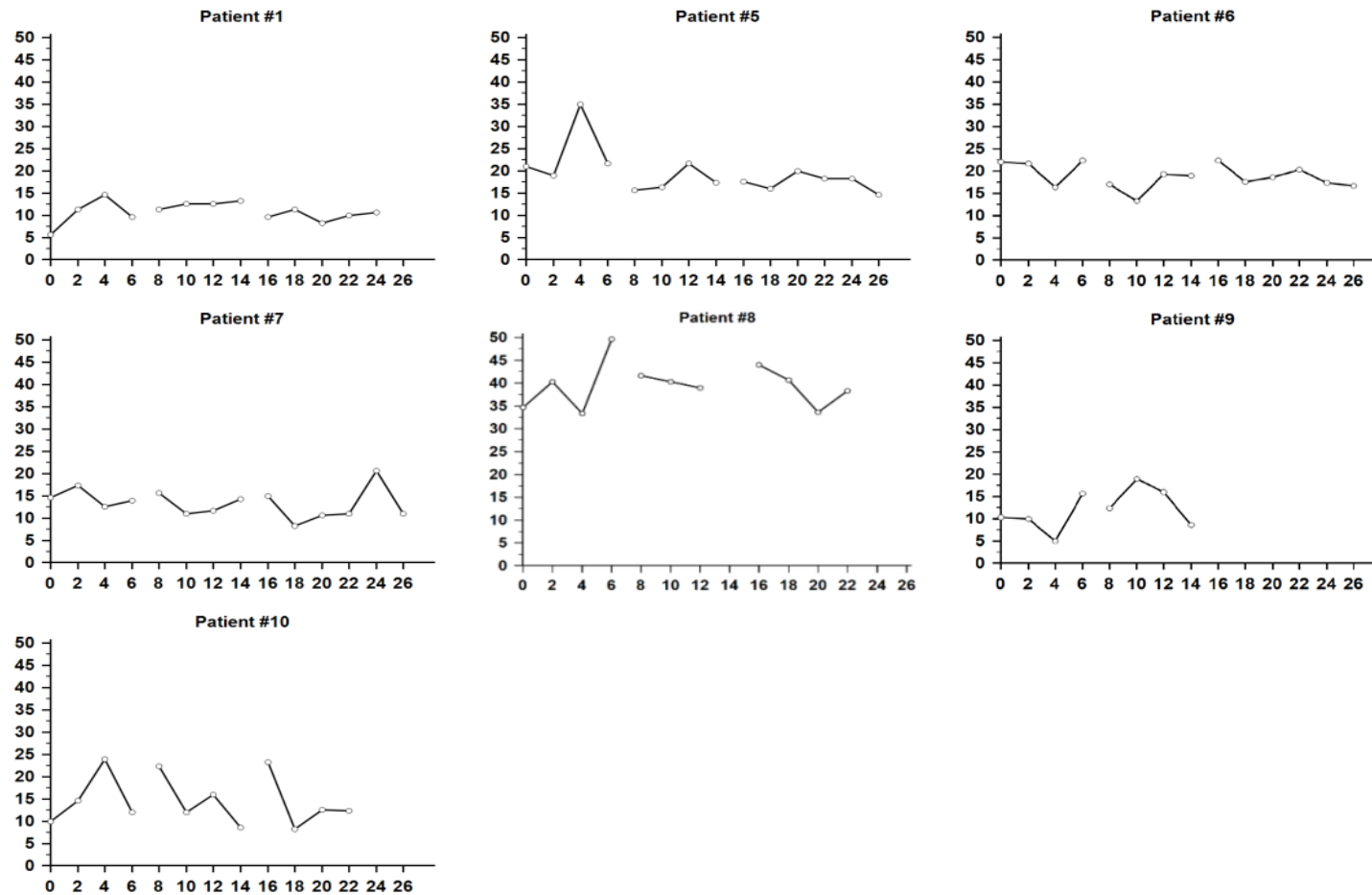


Figure 8.10 Effect of ESWT on Hip Internal Rotation.

Horizontal axes, time in weeks; Week 0 to 6, baseline phase; Week 8 to 14, intervention phase; Week 16 to 24, post-intervention phase; Vertical axes, angle in degrees measured by a universal goniometer.

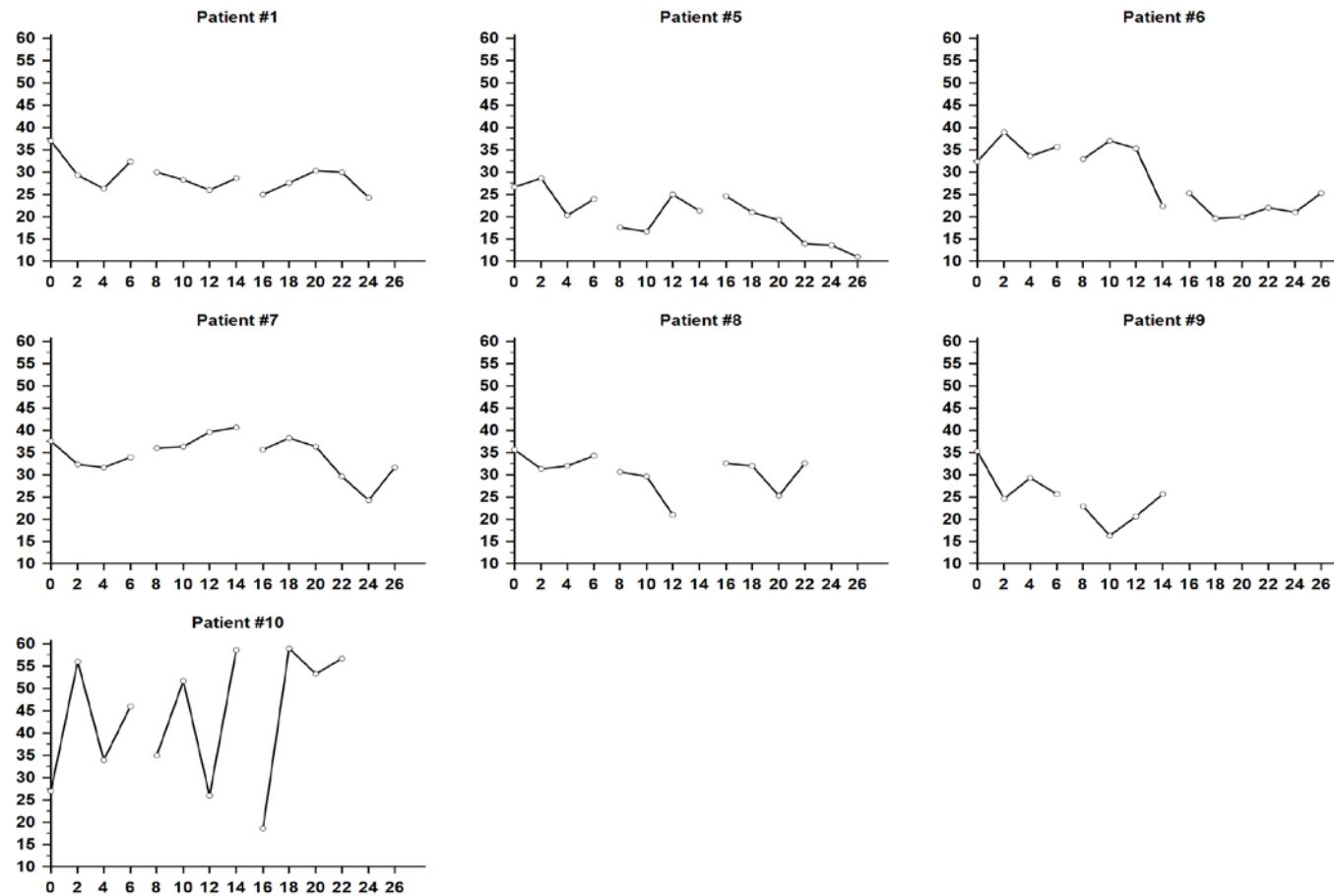


Figure 8.11 Effect of ESWT on Hip External Rotation.

Horizontal axes, time in weeks; Week 0 to 6, baseline phase; Week 8 to 14, intervention phase; Week 16 to 24, post-intervention phase; Vertical axes, angle in degrees measured by a universal goniometer.

Table 8.9
Overall effect of ESWT on Hip Flexion.

Patient	Baseline vs Intervention			Baseline vs Post-intervention		
	Tau	CI 90%	P	Tau	CI 90%	P
1	-0.250	-0.962<>0.462	0.564	-0.050	-0.722<>0.622	0.903
5	0.250	-0.462<>0.962	0.564	0.500	-0.143<>1.143	0.201
6	0.375	-0.337<>1.087	0.387	-0.167	-0.810<>0.476	0.670
7	0.063	-0.650<>0.775	0.885	0.333	-0.310<>0.976	0.394
8	-0.500	-1.275<>0.275	0.289	0.500	-0.212<>1.212	0.248
9	1.000	0.288<>1.712	0.021	Not completed		
10	0.375	-0.337<>1.087	0.387	0.375	-0.337<>1.087	0.387
Overall	0.196	-0.077<>0.468	0.238	0.244	-0.030<>0.519	0.143

Tau, Tau scores; CI 90%, 90% confidence interval; P, P-value

Table 8.10
Overall effect of ESWT on Hip Extension.

Patient	Baseline vs Intervention			Baseline vs Post-intervention		
	Tau	CI 90%	P	Tau	CI 90%	P
1	0.125	-0.587<>0.837	0.773	0.150	-0.522<>0.822	0.713
5	-0.500	-1.212<>0.212	0.248	-0.125	-0.768<>0.518	0.749
6	1.000	0.288<>1.712	0.021	0.250	-0.393<>0.893	0.522
7	0.375	-0.337<>1.087	0.387	0.500	-0.143<>1.143	0.201
8	-0.250	-1.025<>0.525	0.596	0.750	0.038<>1.462	0.083
9	0.750	0.038<>1.462	0.083	Not completed		
10	-0.250	-0.962<>0.462	0.564	0.000	-0.712<>0.712	1.000
Overall	0.166	-0.089<>0.456	0.268	0.251	-0.023<>0.525	0.132

Tau, Tau scores; CI 90%, 90% confidence interval; P, P-value

Table 8.11
Overall effect of ESWT on Hip Abduction.

Patient	Baseline vs Intervention			Baseline vs Post-intervention		
	Tau	CI 90%	P	Tau	CI 90%	P
1	-0.188	-0.900<>0.525	0.665	0.250	-0.422<>0.922	0.540
5	-0.250	-0.962<>0.462	0.564	-0.583	-1.226<>0.060	0.136
6	0.500	-0.212<>1.212	0.248	0.875	0.232<>1.518	0.025
7	0.063	-0.650<>0.775	0.885	0.042	-0.601<>0.685	0.915
8	0.000	-0.775<>0.775	1.000	0.188	-0.525<>0.900	0.665
9	-0.188	-0.900<>0.525	0.665	Not completed		
10	0.875	0.163<>1.587	0.043	0.313	-0.400<>1.025	0.471
Overall	0.117	-0.155<>0.390	0.479	0.178	-0.097<>0.452	0.286

Tau, Tau scores; CI 90%, 90% confidence interval; P, P-value.

Table 8.12
Overall effect of ESWT on Hip Adduction.

Patient	Baseline vs Intervention			Baseline vs Post-intervention		
	Tau	CI 90%	P	Tau	CI 90%	P
1	0.313	-0.400<>1.025	0.471	0.250	-0.422<>0.922	0.540
5	0.125	-0.587<>0.837	0.773	-0.250	-0.893<>0.393	0.522
6	0.625	-0.087<>1.337	0.149	0.500	-0.143<>1.143	0.201
7	-0.500	-1.212<>0.212	0.248	0.083	-0.560<>0.726	0.831
8	-0.333	-1.109<>0.442	0.480	0.250	-0.462<>0.962	0.564
9	0.625	-0.087<>1.337	0.149	Not completed		
10	-0.375	-1.087<>0.337	0.387	0.500	-0.212<>1.212	0.248
Overall	0.073	-0.200<>0.346	0.659	0.217	-0.057<>0.491	0.193

Tau, Tau scores; CI 90%, 90% confidence interval; P, P-value.

Table 8.13
Overall effect of ESWT on Hip Internal Rotation.

Patient	Baseline vs Intervention			Baseline vs Post-intervention		
	Tau	CI 90%	P	Tau	CI 90%	P
1	0.438	-0.275<>1.150	0.312	-0.100	-0.772<>0.572	0.807
5	-0.688	-1.400<>0.025	0.112	-0.917	-1.560<>-0.274	0.019
6	-0.625	-1.337<>0.087	0.149	-0.292	-0.935<>0.351	0.456
7	-0.375	-1.087<>0.337	0.387	-0.417	-1.060<>0.226	0.286
8	0.250	-0.525<>1.025	0.596	0.125	-0.587<>0.837	0.773
9	0.500	-0.212<>1.212	0.248	Not completed		
10	-0.063	-0.775<>0.650	0.885	-0.125	-0.837<>0.587	0.773
Overall	-0.084	-0.357<>0.189	0.611	-0.299	-0.573<>-0.024	0.073

Tau, Tau scores; CI 90%, 90% confidence interval; P, P-value

Table 8.14
Overall effect of ESWT on Hip External Rotation.

Patient	Baseline vs Intervention			Baseline vs Post-intervention		
	Tau	CI 90%	P	Tau	CI 90%	P
1	-0.500	-1.212<>0.212	0.248	-0.500	-1.172<>0.172	0.221
5	-0.625	-1.337<>0.087	0.149	-0.750	-1.393<>-0.107	0.055
6	-0.250	-0.962<>0.462	0.564	-1.000	-1.643<>-0.357	0.011
7	0.750	0.038<>1.462	0.083	-0.125	-0.768<>0.518	0.749
8	-1.000	-1.775<>-0.225	0.034	-0.313	-1.025<>0.400	0.471
9	-0.813	-1.525<>-0.100	0.061	Not completed		
10	0.125	-0.587<>0.837	0.773	0.375	-0.337<>1.087	0.387
Overall	-0.323	-0.595<>-0.050	0.052	-0.399	-0.673<>-0.125	0.017

Tau, Tau scores; CI 90%, 90% confidence interval; P, P-value

8.3.7 Effect of ESWT on NHO as seen on Plain X-ray film

Prior to submission of this thesis only five out of the 11 participants had completed the full study up to and including repeat X-ray, taken at least 6 months post intervention. The remaining participants will be followed up within the required time frame and the complete data set will be published.

The interpretation of the radiographic evidence was carried out by an independent expert radiologist (AL). In the plain X-ray films of the hip and knee at taken at the post-intervention phase it was noted that the radiographic technique was slightly different from that of the earlier X-ray film. At post-intervention, no significant change in size of the areas of heterotopic ossification was noted.

As can be seen in Table 8.15 the percentage correction factors are infinitesimal and when applied to the post-intervention X-rays, no change was noted. This was considered as a potential source of error; the changes however were insignificant and did not change the final measurements.

The X-rays were then analysed visually and any changes were described qualitatively.

Table 8.15
X-ray measurements AP view only with correction factor added.

Patient Code	Baseline Measures (mm)						Post-intervention Measures (mm)						Standardisation		Correction Factor		Post intervention Corrected Measures					
	1	2	3	4	5	6	1	2	3	4	5	6	1	2			1	2	3	4	5	6
2	83	22.8	11.4	10.2			83	25	12.8	10.6			33.8	32.3	1.5	0.04%	83.0	24.9	12.8	10.6		
3	174.4	20.2	55.3	34.3			149.5	20	53.8	31.4			29.8	30.2	-0.4	-0.01%	149.5	20.1	53.8	31.4		
5	102.3	53.5	102	66.7			94.3	62	94.3	65.9			34.3	34.7	-0.4	-0.01%	94.3	62.4	94.3	65.9		
6	113.7	69.3	29.2	10.4	13.9	9.1	113.8	72	28.6	10.6	14	8.6	33.5	33.8	-0.03	-0.01%	113.8	71.9	28.6	10.6	14	8.6
7	101.9	16.1	54.4	17.9	24.6	10.9	104.6	17	52.4	21.3	22.5	14.4	39.4	39.8	-0.4	-0.01%	104.6	16.7	52.4	21.3	22.5	14.4

mm, millimetres

8.3.7.1 Individual Commentaries:

Case #2: Post- intervention X-rays showed erosion in the margin of the ossified areas and slight fragmentation of the lesion. In addition of clarity of the borders and loss of the "cortex" of the lesion could be seen (Plate 8.4).

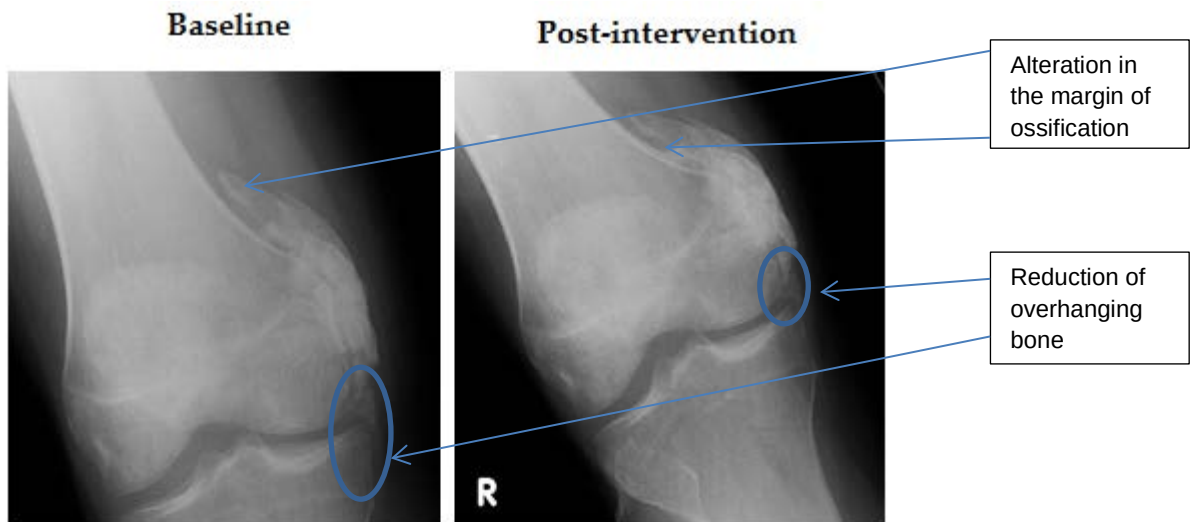


Plate 8.4 Case #2: Baseline and post-intervention X-rays.

Case #3: The visual impression was that the lesion has increased in size between the two studies (Plate 8.5)

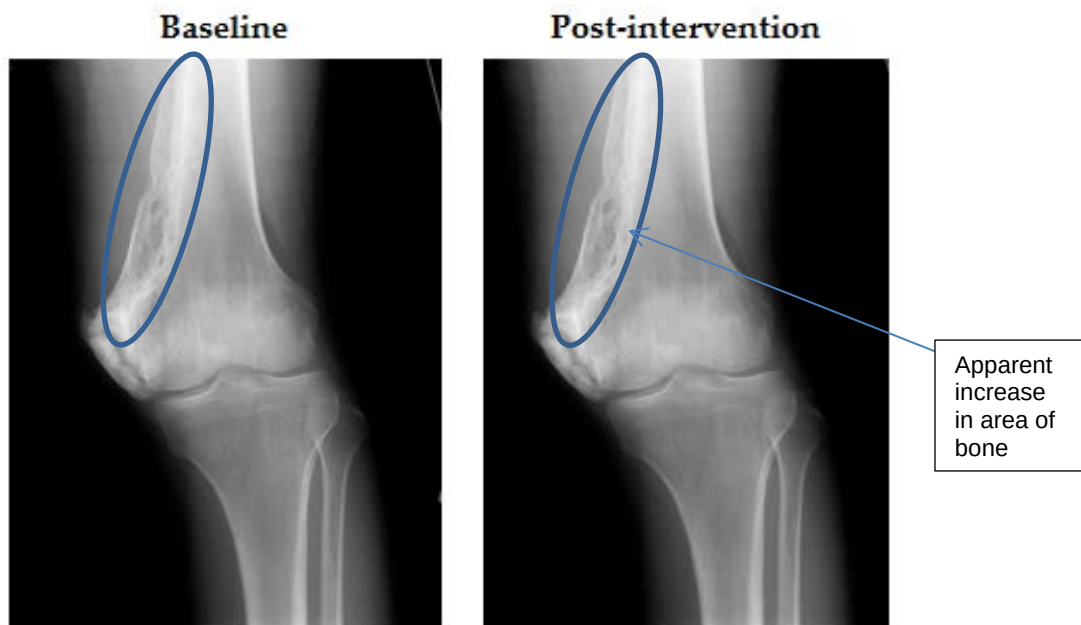


Plate 8.5 Case #3: Baseline and post-intervention X-rays.

Case #5: Very similar techniques for both B and PI X-rays. X-rays showed a definite irregularity of the upper border of the lesion under the femoral neck on the post intervention X-ray. Lower border of the lesion is fragmented suggesting possible erosion of the lesion (Plate 8.6).

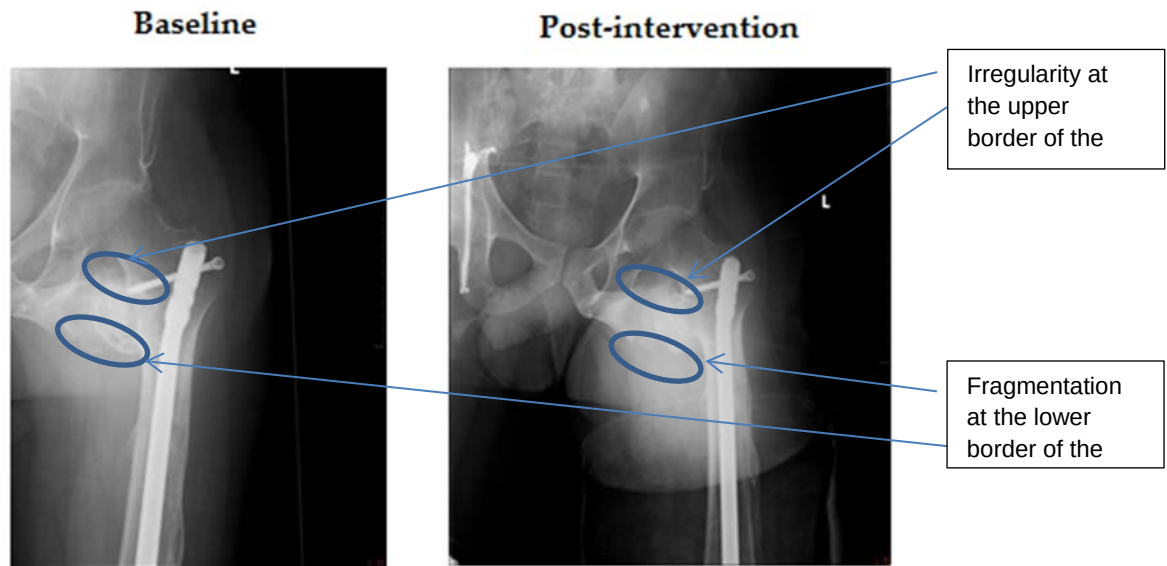


Plate 8.6 Case #5: Baseline and post-intervention X-rays.

Case #6: The lesion is very irregular and visually it would seem that on the post-intervention study there is some erosion around the lesion. (Plate 8.7)

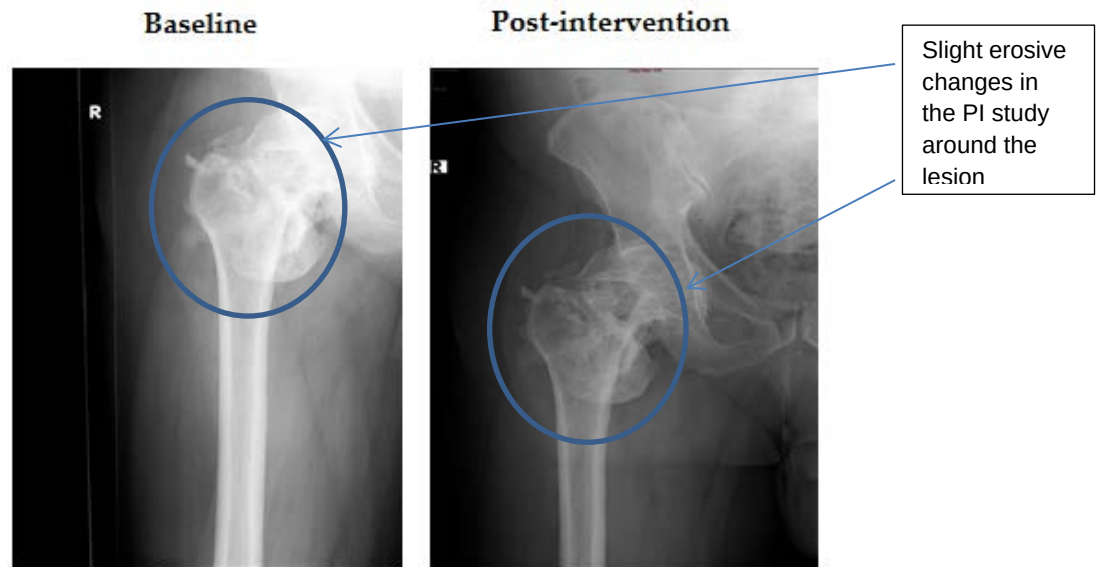


Plate 8.7 Case #6: Base-line and post-intervention X-rays.

Case # 7: On the post-intervention (PI) study of the right hip the margins of the lesions are definitely less well defined inferiorly and around the femoral neck. This is also the case around the inferior margin of the gluteal ossification. This is of interest because the technical differences of the PI study give the image more contrast and a higher definition of the areas mentioned than would have been expected. (Plate 8.8)

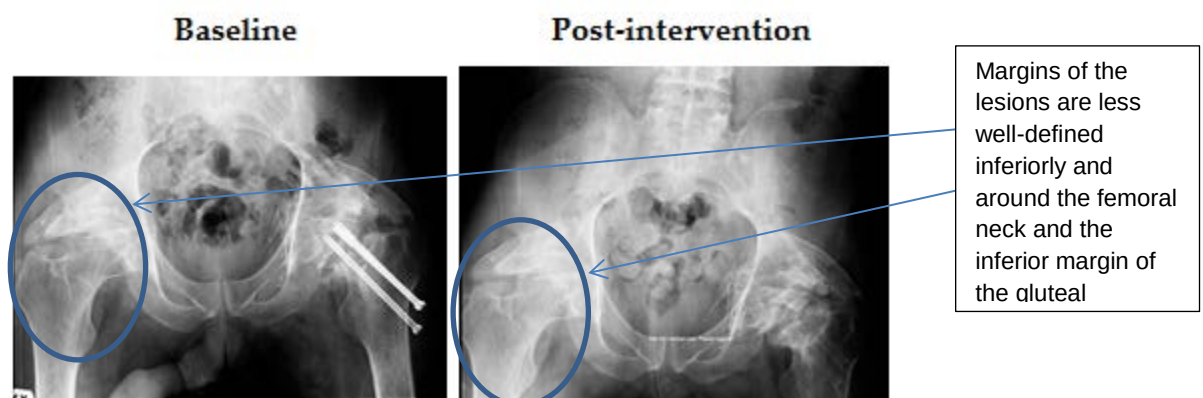


Plate 8.8 Case #7: Baseline and post-intervention X-rays.

8.3.8 Effect of ESWT on Gait Scores in Ambulant Patients

Five out of the 11 participants were non-walkers; of the 6 walkers one was lost to follow-up. Gait parameters were measured at base-line (week 0) and post intervention (week 38). Of the five remaining walkers three showed improvement in gait velocity and results worsened in two participants (Table 8.16). Four participants improved in stride length, and results worsened in one participant (Table 8.16). Finally, two out of four walkers improved in the distance covered in the 6 minute walk and the results worsened in two participants (Table 8.16). Overall, all changes recorded were only minor with percentage change (D%)<10 (Table 8.16).

Table 8.16
Gait parameters.

Patient	Gait velocity (m/s)			Stride length (m)			6 min walk (m)		
	B	PI	D%	B	PI	D%	B	PI	D%
1	1.23	1.11	-10.31	0.58	0.56	-2.35	409	427	4.40
2	0.83	0.86	4.44	0.46	0.51	10.17	300	442	47.33
3	0.42	0.53	25.75	0.35	0.38	10.26	Unable to complete		
4	1.27	Lost to follow-up		0.67	Lost to follow-up		467	Lost to follow-up	
5	Non – walker								
6	1.03	1.07	3.35	0.57	0.59	3.92	412	378	-8.25
7	Non – walker								
8	0.68	0.58	-15.05	0.48	0.49	2.08	336	286	-14.88
9	Non – walker								
10	Non – walker								
11	Non – walker								
Overall	0.91±0.33	0.83±0.27	1.64±15.92	0.52±0.11	0.51±0.08	4.82±5.43	385±66	383±70	7.15±27.96

B, baseline; PI, post-intervention; D%, percent change relative to baseline; Overall, arithmetic mean ± standard deviation (SD); m, metres; m/s, metres per second

8.3.9 Effect of ESWT on Functional Independence Measure (FIM)

Apart from one participant (Case #3) who had a reduction in his motor FIM score due to an unrelated event, the remaining participants showed minor changes only in their FIM scores (Table 8.17).

Table 8.17
Motor FIM Scores.

Case	B Week 0	PI Week 16	D% Week 16	PI Week 26	D% Week 26	PI Week 38	D% Week 38
1	79	79	0	79	0	Not completed	
2	66	66	0	66	0	64	-3
3	83	64	-23	68	-18	Not completed	
4	75	Lost to follow -up					
5	56	56	0	58	4	Not completed	
6	86	86	0	83	-4	84	-2
7	51	58	14	54	6	57	12
8	73	71	-3	75	3	Not completed	
9	25	Not completed					
10	13	13	0	13	0	Not completed	
11	29	29	0	29	0	Not completed	
Overall	58±25	58±23	-1±9	58±23	-1±7	68±14	2±8

B, baseline; PI, post-intervention; D%, percent change relative to baseline; Overall, arithmetic mean ± standard deviation (SD); FIM, functional independence measure; FIM motor scores range from 13 (total dependence) to 91 (total independence (Appendix 1C)

8.3.9.1 *Effect of ESWT on European Quality of Life 5–Dimensions Questionnaire Scores (EQ-5D)*

The EQ-5D scores demonstrated marked inconsistency i.e. one participant had ~900% improvement on the quality of life scale, whilst showing a negative value on the self-assessment questionnaire. Thus, there is difficulty with the interpretation of EQ-5D scores in this specific group of severe head injured patients (Table 8.18).

Table 8.18
EQ-5D Scores.

Patient	EQ-5D (1/25)			EQ-5D (1/100)		
	B	PI	D%	B	PI	D%
1	19	18	-5	5	50	900
2	15	17	13	50	30	-40
3	14	19	36	60	45	-25
4	8	Lost to follow-up		70	Lost to follow-up	
5	14	20	43	40	37	-7.50
6	12	14	17	90	90	0.00
7	16	14	-13	60	70	16.67
8	13	16	23	85	85	0.00
9	23	Not completed		0	Not completed	
10	20	19	-5	25	25	0.00
11	12	12	0.00	98	98	0.00
Overall	15±4	17±3	12±19	53±33	59±27	94±303

B, baseline; PI, post-intervention; D%, percent change relative to baseline; Overall, arithmetic mean ± standard deviation (SD)

8.3.10 Serum Alkaline Phosphatase (SAP) Levels

SAP levels were measured at baseline phase (week 0), intervention phase (week 10), and post-intervention phase (week 22). Circulating SAP levels remained within normal limits throughout the study in all but one patient, who fell at home just prior to the study period and fractured the non-treated hip (Table 8.19).

Table 8.19

SAP levels (units per litre).

Patient	B Week 0	I Week 10	D% Week 10	PI Week 22	D% Week 22
1	79	96	22	96	22
2	72	72	0	57	-21
3	112	98	-13	Data unavailable	
4	107	107	0	80	-25
5	156	167	7	128	-18
6	95	98	3	117	23
7	149	150	1	165	11
8	53	Data unavailable			
9	108	111	3	Not completed	
10	Data unavailable				
11	115	115	0	Not completed	
Overall	105±32	113±29	3±9	107±38	-1±22

B, baseline; I, intervention; PI, post-intervention; D%, percent change relative to baseline; Overall, arithmetic mean ± standard deviation (SD). The normative value for alkaline phosphatase (ALP) is 53 - 128 units per litre (U/L) in a 20 to 50 year-old man and 42 -98 U/L in a 20 to 50 year-old woman. Adults over 61 years have normative values of ALP of 51-153 U/L

8.4 Discussion

This series of single case research studies was conducted in order to examine the effects of ESWT applied to chronic NHO in the hip or knee joint of patients following TBI. The results obtained from this trial largely confirmed those found in the previously reported single case study (Reznik, et al., 2013a); despite fluctuations, overall, pain was significantly decreased, and functional reach, as a measure of balance, also showed overall significant improvement. Flexion at the knee joint showed significant improvement, but not extension. In the hip joint there was a trend towards improvement in flexion, extension, abduction and adduction, although external rotation showed significant overall reduction in range after ESWT. The gait results were variable, with some participants improving on one parameter while worsening on another. It is however, of interest to note that one participant began walking without an aid, and a second, previously a non-walker, began to walk post-intervention. These results demonstrate an important feature of the single case research design, i.e. that the effects in a specific person can be evaluated and it can be ascertained whether they are a responder or non-responder to the intervention. This is an advantage over a randomised controlled trial where group results only tend to be reported, and it is difficult to determine those for whom a treatment is effective. The SAP levels were taken as a safety measure in order to ascertain if the treatment triggered a further ossification process. Levels remained within normative values throughout the study establishing the safety of the intervention from this aspect. As discussed earlier only two patients were on medications for intractable pain; in these two patients, medications were either reduced or discontinued. No long-term adverse effects were reported during the study.

The significant effect of ESWT on pain is an important finding of this study. The pain presentation within our group of TBI patients was very variable. Some participants complained of pain only when performing a functional activity, others complained of pain only on passive movement of the affected joint and some complained of intractable pain throughout the day. In those patients with pain on movement, it is possible that some peripheral nociceptive mechanisms were involved (Latremoliere & Woolf 2009). In those with intractable pain, their pain could be classified as neuropathic pain (Merskey & Bogduk, 1994; Treed, 2008). In this study the pain assessment focussed on pain intensity rather than the pain quality, which is often the major descriptor of neuropathic pain. However it is doubtful that this particular patient group would be able

to provide valid descriptors of their pain. It is well documented that chronic pain causes changes in the central nervous system (DeLeo, Tanga, & Tawfik, 2004). When there is damage to the nervous system, nociceptive activity is generated within the nervous system rather than at the peripheral nociceptor. Damage and disease also often affects larger myelinated afferent neurons as well as the thinly myelinated and unmyelinated nociceptive afferents. Ectopic neuronal activity arising at some point along the axon rather than at the peripheral receptor seems to be one of the key mechanisms for triggering neuropathic pain (Devor, 1991). This atypical neuronal activity may also initiate central sensitisation but importantly, damage to the nervous system will also trigger some degree of neuroanatomical reorganisation within the nervous system (Woolf & Manion, 1999). In a recent review paper on the role of cytokines in mediating spinal neuron-non-neuronal cell communication in neuropathic pain mechanisms, Clark et al (2013) concluded that cytokines and chemokines released by neurons, microglia, astrocytes, macrophages and T cells may play pro- or anti-nociceptive roles at the first pain synapse under neuropathic pain conditions (Clark, Old & Malcangio, 2013). It is possible that ESWT, through reduction of SP levels, may have reduced the level of inflammatory cytokines which led to the observed reduction in pain. ESWT could have reduced a nociceptive trigger, and because the patients were able to move more freely, a reorganisation of the pain matrix could occur.

The improvement seen in Functional Reach (FR) represents an improvement in balance. This may be also attributed to the reduction in pain. Gill and Callaghan (1998) suggested that pain displaces the normal signals coming from muscles and sensory organs and in doing so delays balance reactions.

The results obtained in this series of single case research studies demonstrated a significant overall improvement in range of knee flexion. There was a weak effect on the range of knee extension and in the range of hip movements of flexion, extension, abduction and adduction. Overall internal rotation at the hip showed no improvement and the range of external rotation was significantly reduced. The losses of ROM at the hip varied between 3 and 12 arc degrees (°) of external rotation; 3° is a negligible loss, although 12° represents a loss of 40% of normal range. This would indicate an adverse response, as regards ROM, in one participant. This adverse response was not however reflected in either the patient's pain or functional assessment (MFR). No functional

losses were recorded and FR showed statistical improvement overall. The mechanisms underlying the differential effects of the EWST at the knee and hip require further investigation. This result also reflects what was found in our meta-analysis (Reznik et al., 2013b). It may well indicate the difficulty in accessing NHO at the hip-joint due to the thickness of the overlying tissues, particularly the adductor muscle. It may also be due to the deeper position of the NHO at and around the hip joint. In order to address these problems it might be necessary to apply higher dosages of ESWT when treating the larger joints.

The second X-ray studies at approximately six months post intervention, showed no change in size of the areas of heterotopic ossification, and the changes shown on X-ray were therefore described qualitatively. Some radiographs showed erosion and marginal absorption of bone around the NHO deposits. Consequently size alone is not going to be an acceptable way of measuring NHO, because it is doubtful if ESWT will cause the bony lesion to break up and reabsorb, a physiological event that will take much longer than six months. The results obtained in this study suggest that a second round of treatment may be warranted. Although qualitatively there appeared to be a change in bone density, measurement of bone density is fraught with difficulty when using conventional X-ray techniques. Even with digital images problems arise because of uncertainties as to the reproducibility of the radiographic exposure, or whether the patient is simply developing osteopaenia due to some other cause (steroids, lack of mobility, etc.). Future studies may benefit by using Dual Energy X-ray Absorptiometry (DXA, previously DEXA scanning) of the lesions and using another nearby bone, such as the femoral shaft, as a control. Although no radiological evidence was seen in this study, a recent research paper by C-J Wang et al (2011) on an osteoarthritic rat model, demonstrated that a single dose of ESWT improved the subchondral bone remodelling and decreased the articular cartilage degradation possibly preventing or retarding osteoarthritic changes (C-J. Wang et al., 2011).

8.5 Limitations of the Study

This series of single case research studies comprised a relatively small number of participants and of females in particular. Although the male: female ratio is consistent with that found within this patient population the small number of female participants does limit the generalizability of this study.

The results obtained on the Functional Independence Measure (FIM) scores demonstrated little or no change throughout the study. Although the FIM has definite ceiling effects, particularly in the TBI population (Hall et al., 1996) it has been shown to be reliable and to be able to detect changes over time in this patient population (van Baalen et al., 2006). In order to reduce the ceiling effect of the FIM alone, it has been recommended, for TBI patients of one year post injury, that the FIM be combined with an additional 12 items, the Functional Assessment Measure (FAM) (Gurka et al., 1999; van Baalen et al., 2006).

As a quality of life measure the EQ-5D demonstrated a lack of validity for this particular patient group. Many of the participants had great difficulty in understanding and answering the questions in the self-assessment questionnaire and in many cases there was little or no relationship between the responses on the questionnaire and the quality of life scale. Although it has been recommended for use in the TBI population (Nichol et al., 2011) and has also been validated in the Hebrew speaking population (Horowitz, Abadi-Korek, Shani, & Shemer, 2010) our results did not demonstrate it to be a valid measure of quality of life for this group of patients. This was an unexpected finding. A recent systematic review on health-related quality of life after TBI (Polinder, Haagsma, van Klaveren, Steyerberg & van Beeck, 2015) concluded that there are still major gaps in our understanding of how to measure the impact of TBI on personal and population health. Polinder et al (2015) recommend the use of the SF-36 in combination with a TBI-specific instrument such as the Quality of Life after Brain Injury (QOLIBRI). Van Baalen and colleagues (2006), in their study on the reliability and sensitivity of suitable outcome measures for the TBI population one year post injury, recommend as quality of life scales, the Sickness Impact Profile-68 (SIP-68) or the Dartmouth Coop Functional Health Assessment Charts/Wonca (Coop). Since the EQ-5D, with five questions proved difficult to use in our study, it is unlikely that our patients would have found the SIP-68, with 68 questions, any easier. The Dartmouth Charts, with pictorial descriptors, should be investigated further, as the TBI population “at risk” for the development of NHO are most likely to be those with serious head injuries (Chapters 2 and 5) and all quality of life measures may be difficult to apply in this group.

It is important also to note that there are many non-compliance issues within a group of severe TBI patients, all of whom had additional cognitive problems, some demonstrating aggressive tendencies, some impulsivity and others forgetfulness and/or apathy. As a consequence of the lack of compliance only eight of the 11 patients have to date completed the full trial and only five of the 11 have had pre- and post-intervention X-rays. As a result, ethics approval for this trial has been extended, and when all patients have completed the results of the study will be published.

As stated in the earlier part of this chapter, this trial was conducted as a series of single case research studies. Given the practical limitations of a more traditional randomised control trial (RCT) with this relatively rare complication of TBI patients, the single – case experimental design allows us to draw conclusions about the effects of a specific treatment intervention based upon the responses of a single patient under controlled conditions (Portnoy & Watkins, 2008). Repeated measures were taken at baseline, intervention and post-intervention phases. However no “sham” trial was considered feasible with this patient group and the possibility of the placebo effect must be taken into account.

Observation bias (the Hawthorne Effect) is the process where human subjects of an experiment change their behaviour simply because they are being studied (McCarney et al., 2007). It is possible, as indeed with any intervention study, that this phenomenon may cause bias. However the Hawthorne Effect leads to only short-term changes in behaviour. The advantage of the single case research design is that repeated measures enable observation of fluctuations in behaviour as well as trends over time. In this study, repeated observations of different outcome measures were able to show lasting changes over time. In order to minimise bias the assessments were undertaken by an independent assessor who was blinded to the results. The patients were also assessed individually, so that no group pressure was exerted and the two week period between assessments and treatments reduced the intensity of the observations.

8.6 Key Points

- This small series of single case research studies suggests that ESWT could be an effective non-invasive intervention for the treatment of chronic NHO in TBI patients.
- No serious adverse effects were reported. There was a marked reduction in hip external rotation in one participant following treatment.
- Application of ESWT at the hip may require an adjustment in dose.
- Further replication of our findings by other groups using our protocol would enhance the evidence for this intervention.

Chapter 9. Summary Discussion, Clinical Recommendations and Future Directions

9.1 Introduction

The previous chapters have reviewed the literature on Neurogenic Heterotopic Ossification (NHO), Extracorporeal Shockwave Therapy (ESWT) and the use of ESWT in the management/treatment of NHO. In addition a single case study and a series of further single case research studies were undertaken to provide evidence that ESWT may be an effective novel intervention for the management/treatment of NHO in traumatic brain injury (TBI) patients. In this concluding chapter I will summarise my findings and offer clinical recommendations and possible future directions for the use of ESWT in the treatment of NHO.

9.2 Summary Discussion

The overall objective of this research was to investigate the utility and effectiveness of a new protocol for the management /treatment of NHO in patients with TBI.

By exploring the prevalence, risk factors, and current clinical management of NHO, it became clear that NHO represents a considerably variable and often neglected complication of neurotrauma such as TBI and TSCI. The findings of this study (Chapter 5) indicate that risk factors associated with NHO in TBI and TSCI patients are distinct, apart from deep vein thrombosis and/ or pulmonary embolus which seem to be the only common NHO-associated risk factors in TBI and TSCI patients (Reznik, et al, 2014). NHO has been reported to occur almost exclusively in the more severe cases of TBI (Reznik, et al., 2014), and in the TSCI patients it was found to be more common in the motor complete, but sensory incomplete patients (AIS B) (Reznik, et al., 2014). The prevalence of NHO in patients admitted to specialised units has been estimated to be approximately 4% and 11% in TBI and TSCI patients respectively (Reznik, et al, 2014). In specialised units NHO is usually diagnosed only when it becomes clinically significant and the condition appears to be undocumented in patients with neurotrauma who are admitted to non-specialised units within Australia. The reason that NHO remains undocumented in the tertiary hospitals in Australia may possibly be due to the coding system used throughout Australian hospitals (ICD-10-AM) not being primarily

designed for documentation of the TBI/TSCI complications (Reznik, et al, 2015). The actual prevalence of the condition is therefore likely to be underestimated.

Since the pathophysiological mechanisms associated with the development of NHO are complex (Chapter 2), once diagnosed, the treatment options remain limited. Only NSAIDs or surgery or a combination of the two appears to provide some beneficial effects against developing or established NHO (Banovac et al, 2004; Melamed et al, 2002). Since NSAIDs appear to provide mainly a prophylactic benefit (Banovac et al., 2004) and surgery carries with it many adverse side effects (Meiners, et al., 1997) there would seem, therefore, to be a need to investigate further non-invasive and safe options for the treatment of NHO. ESWT appears to be one such option. The biological effects associated with the application of ESWT include stimulation of tissue healing, disintegration of calcium deposits, and suppression of pain (Speed, 2004), and the method has been successfully used in the treatment of a range of chronic musculoskeletal conditions for over two decades (Furia, 2008; Haake et al, 2003; Ioppolo et al, 2014, 2013; Ogden, 2004; Rompe et al, 1996, 1998; Speed, 2013; Valchanou and Michailov, 1991; C-J. Wang, 2012). In his recent review on the use of ESWT in musculoskeletal disorders C-J. Wang (2012) documented only minor, temporary, adverse effects such as reports of pain or discomfort during treatment, possible minor skin irritation and occasional numbness or paraesthesia. In the series of single case research studies reported upon in this thesis, minor adverse effects of a slight increase in pain immediately following treatment were reported in two cases, and a reduction in hip external rotation in one case (Chapter 8). Although all dosages were administered in the high energy range (i.e. $EFD > 0.12 \text{ mJ/mm}^2$) they were not given at levels above the patients' pain threshold.

The role of ESWT in the clinical management of patients with NHO has been relatively little studied (Brissot et al, 2005; Buselli et al, 2009; Reznik et al, 2013a; Torrance and DeGraauw, 2011). A meta-analysis of these individual studies suggested that a regime of four applications of ESWT over the affected joint or muscle was associated with an improvement in range of motion (ROM) of the joint, more extensibility of the muscle and a reduction in pain (Reznik et al., 2013b). The effect sizes however, did not reach statistical significance (Reznik et al, 2013b). Considering that the beneficial effects of

ESWT are also dose-dependent (Zhang et al, 2014), the dose heterogeneity between studies may have biased the results obtained (Reznik et al, 2013b).

The culmination of this thesis was the series of single case research studies conducted to investigate the effects of ESWT on NHO in patients with TBI. The initial single case study, which reported on the use of ESWT in a chronic TBI patient with recurrent NHO at the hip, suggested that ESWT may be a useful clinical intervention (Reznik et al, 2013a). This successful case report provided the proof-of-concept for the larger series of single case research studies, the results of which are presented and discussed in Chapter 8 of this thesis. The trial was carried out only on a population of TBI patients with chronic NHO in order to ensure homogeneity within the patient populations, thus avoiding the possible biases of a more heterogeneous population with neurotrauma.

The use of a single case experimental design rather than a randomised controlled trial (RCT) to identify the effectiveness of ESWT on NHO deserves special comment. The clinical research community promotes the RCT as the “gold standard” for investigations of efficacy of clinical interventions. In order to enable a causal association to be made between interventions and outcomes, the design of a RCT minimises threats to internal validity by minimising sources of bias (e.g. through randomisation, allocation concealment, blinded assessment). However RCTs may not always be feasible, especially with disorders of low prevalence where it would be difficult to recruit a sufficiently large number of participants for adequate statistical power for between-group comparisons. Furthermore, identification of responders and non-responders to the intervention may be unclear when only group means and associated effect sizes are reported. Since NHO as a complication of TBI is relatively rare (Reznik et al, 2013a; Reznik et al, 2014), an RCT was not a practical option for investigation of the efficacy of ESWT on NHO.

Single subject experimental designs have a long history in psychology, education and rehabilitation (Kratochwill et al. 2010; Logan Hickman, Harris, & Heriza, 2008). These designs involve repeated systematic measurement of a dependent variable(s) (e.g. ROM, pain) before, during and after the active manipulation of an independent variable (e.g. administration of ESWT). The different conditions of the independent variables are called phases (e.g. baseline phase, intervention phase). An individual case is the unit of intervention and the unit of data analysis. Each case provides its own control for the

purpose of comparison (i.e. outcome measures pre- and post-intervention). Kratochwill et al. (2010) highlight the need to control threats to internal validity in single case designs. Kratochwill & Levin (2010) suggest the incorporation of various forms of randomization in the traditional design structure of single case designs; however this would have been impractical with an intervention such as ESWT. Another method of controlling threats to internal validity is replication of the treatment effect. In the trial of ESWT, replication of the effect within a participant was not possible, since repeated administration of ESWT beyond the four doses provided within a relatively short time frame may not be safe. Moreover, one of the outcome measures was change in the NHO on plane X-ray six months following intervention, making the “washout” period impractical to factor in a second treatment of ESWT. Therefore the study design incorporated replication of the treatment effect between participants. A further strength of this study was the use of the Tau-U index for statistical analysis in addition to the traditional visual analysis; this index measures data non-overlap between baseline and treatment phases, and also controls for baseline trend (Parker et al., 2011).

Finally, while single case research designs have typically not featured in traditional Levels of Evidence tables (e.g. Sackett, Rosenberg, Gray, Haynes, & Richardson, 2007), there have been recent efforts to evaluate the quality of this type of study (Logan et al., 2008; Tate et al., 2013). Based on criteria suggested by Logan et al (2007) this study scored 12.5 out of a possible total of 14 marks, putting it in the category of a strong single-subject research design (SSRD).(Table 9.1).

Table 9.1

Quality analysis of single-subject research design (SSRD) methods applied to the investigation of ESWT.

Criteria	Score
Description of Participants and Settings	
4. Was/were the participant(s) sufficiently well described to allow comparison with other studies?	Yes
Independent Variable	
5. Were the independent variables operationally defined to allow replication?	Yes
6. Were intervention conditions operationally defined to allow replication?	Yes
Dependent Variable	
7. Were the dependent variables operationally defined as dependent measures?	Yes
8. Was interrater or intrarater reliability of the dependent measures assessed before and during each phase of the study?	Yes
a. Was the outcome assessor unaware of the phase of the study (intervention vs control) in which the participant was involved?	No
9. Was stability of the data demonstrated on the baseline, namely lack of variability or a trend opposite to the direction one would expect after application of the intervention?	Yes
Design	
10. Was the type of SSRD clearly and correctly stated?	Yes
11. Were there an adequate number of data points (minimum of five) for each participant?	Four data points only
12. Were the effects of the intervention replicated across three or more subjects?	Yes
Analysis	
13. Did the investigators conduct and report appropriate visual analysis, e.g. level, trend and variability?	Yes
14. Did the graphs used for visual analysis follow standard conventions?	Yes
15. Did the investigators report tests of statistical analysis?	Yes
16. Were all criteria for the statistical analysis met?	Yes
Total Score	12.5

(Modified from Logan, et al., 2008)

Categories used: Strong, 11-14; Moderate, 7-10; Weak, <7

The clinical study had a number of limitations. The sample size was relatively small because of the low prevalence of the condition, although sufficiently large to estimate clinically significant effects. Furthermore, most participants were men in the younger age groups limiting the generalisability of the findings to other groups such as women or patients of older age with TBI. The findings of this case series, however, should be replicated in further studies in the TBI population, as well as in other specific neurotrauma groups, such as TSCI patients.

Radiographs are still considered to be the most efficient method of screening for NHO (Seipal et al., 2012). The post intervention study showed no significant change in size of the areas of heterotopic ossification was demonstrated, although qualitative changes with erosion and marginal absorption of the bone were detected on three out of the five radiographs available for examination (Chapter 8). This suggests early changes after treatment; however the time scale may be too soon to show measurable alteration in appearance and long term follow-up examinations will be required for further assessment.

9.3 Clinical Recommendations

A number of clinical recommendations can be made on the basis of the studies reported in this thesis:

1. The ICD-10-AM (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification*) which refers to the Australian modification of the World Health Organization (WHO) ICD-10 base classification system should be reviewed in order to incorporate NHO as a complication of TBI and/or TSCI.
2. The possibility of the adoption of a simple, inexpensive testing procedure for NHO such as bedside ultrasound, to allow for early diagnosis and treatment of this complication in “at-risk” patients (Falsetti et al, 2011) should be investigated.
3. Educational workshops and/or packages should be made available to all staff involved in the treatment of neurotrauma patients, both in specialised and non-

specialised units, in order to create awareness of those patients “at-risk” of developing NHO.

4. In those TBI patients with mature NHO at the hip or knee, ESWT should be considered as a treatment option, although adjustment of the dose for the hip may be necessary (see below). Further replication of our findings by other groups using our protocol would enhance the evidence for this intervention.

9.3.1 Protocol for use of ESWT

In the series of single case research studies reported in this thesis, the inclusion criteria were that the patient be more than 18 years of age; have sustained a traumatic brain injury; be diagnosed with NHO around the hip or knee for a period of more than one year; and with stable serum alkaline phosphatase (SAP) levels at the time of recruitment. Patients were excluded if they were pregnant, or suffering from rheumatoid arthritis, ankylosing spondylitis or femoral/pelvic fractures at the time of recruitment. Therefore, the results can only be generalised to patients who fit these criteria.

The procedure for the application of ESWT for NHO at the hip or the knee was as follows:

1. A plane X-ray of the site of NHO, necessary to calculate its area.
2. Dosage was calculated from the size of the NHO as seen on X-ray and the area to be treated marked into one cm² zones. The number of shocks per zone was dependent upon the number of zones to be treated but did not exceed 500. A maximum of 3000 shocks/treatment.
3. Four doses of high energy flux density (EFD>0.12mJ/mm²) two weeks (±3 days) apart over a period of 6-8 weeks are recommended by the manufacturer
4. Radiographs should be taken at six months and then again at 12 months post-intervention in order to ascertain physiological changes.

The complete protocol for this clinical trial is available on-line at ClinicalTrials.gov Identifier NCT02331628.

9.4 Future directions

This series of single case research studies was the first of its kind to be conducted on a group of TBI patients. The results achieved offer a number of possible future directions:

1. Overall pain was reduced significantly and improvement in knee flexion also reached significant levels. Movements at the hip were not significantly improved possibly due to the deeper positioning of the NHO. Since the effects of ESWT are known to be dose –dependent, future studies, using higher EFDs at the hip, are recommended (Zhang et al., 2014).
2. The possibility of an additional application of ESWT depending upon the affected joint should be explored. Although up until now four doses of ESWT have been the maximum and the treatment has not been repeated, it is possible that with an additional four doses repeated following the recommended six-month “wash-out” period the treatment may prove more effective on NHO at large joints such as the hip.
3. The prevalence of NHO in the TSCI patient is almost three times higher than in the TBI patient. It is therefore important that the effectiveness of ESWT on chronic NHO following TSCI be investigated.
4. Further questions were also raised during this trial as to the possible use of ESWT prophylactically in the prevention of NHO in those “at-risk” patient groups. This is an additional line of enquiry for future research.
5. Since the causative factors of NHO remain unknown, future research should also focus on trying to identify these factors. It has been suggested by many authors (Bidner et al., 1990; Gautschi et al., 2009; McCarthy & Sundaram, 2009; Weiss et al., 1979) that the trauma itself may be the trigger; identification of a genetic marker in susceptible individuals may lead to elimination of NHO rather than management or treatment.

Epilogue

Although most PhD candidates refer to their period of study as a journey, my goal in undertaking this PhD was not only to add to the body of literature available on this subject but to offer a non-invasive solution, with minimal side effects, to patients with this complication of an already life-changing event. Throughout my journey I have received numerous emails from people all over the world who are suffering from HO as a complication of TBI, TSCI, burns, or THA, asking my opinion of the possibility of using ESWT as an intervention to reduce their signs and symptoms. Most of the people making these enquiries have read my published papers. In each case I have guided them to discuss the treatment of HO using ESWT with their treating physicians and have also directed them to the Clinical Trial website where the protocol for this series of single case research studies is available on-line. One young TSCI patient (C4/5 incomplete lesion) is about to undergo this treatment under the auspices of his treating physician and physical therapist.

My journey has been worthwhile.

JER November 2015

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Appendix 1: Assessment Charts

Appendix 1A: Frankel Scale

Acute Spinal Cord Injury - Frankel Classification Grading System

Grade A	Complete neurological injury - no motor or sensory function clinically detected below the level of the injury.
Grade B	Preserved sensation only - no motor function clinically detected below the level of the injury; sensory function remains below the level of the injury but may include only partial function (sacral sparing qualifies as preserved sensation).
Grade C	Preserved motor non-functional - some motor function observed below the level of the injury, but is of no practical use to the patient.
Grade D	Preserved motor function - useful motor function below the level of the injury; patient can move lower limbs and walk with or without aid, but does not have a normal gait or strength in all motor groups.
Grade E	Normal motor - no clinically detected abnormality in motor or sensory function with normal sphincter function; abnormal reflexes and subjective sensory abnormalities may be present.

Reference: Donovan, W. H., Brown, D. J., Ditunno Jr, J. F., Dollfus, P., & Frankel, H. L. (1997). *Neurological issues. Spinal Co*

Appendix 1B: AIS

ASIA IMPAIRMENT SCALE

- ‘A’ being complete and having no sensory or motor function preserved in the sacral segments of S4 to S5.
- ‘B’, sensory incomplete, is having sensation but not motor function reserved below the neurological level and includes the sacral segments S4-S5 (light touch, pinprick, at S4-S5: or deep anal pressure (DAP)), **and** no motor function is preserved more than three levels below the motor level on either side of the body.
- ‘C’, motor incomplete, is motor function preserved below the neurological level, and more than half of the key muscle functions below the single neurological level of the injury (NLI) have a muscle grade of less than 3 (grades 0-2).
- ‘D’ is also motor incomplete and has motor function preserved below the neurological level, and at least half of the key muscle functions below the NLI have a muscle grade equal or greater than 3.
- ‘E’ is classified when sensation and motor function, as tested with the ISNCSCI, are graded as normal in all segments and the patient has had prior SCI deficits. (Someone without an initial SCI does not receive an AIS grade)

Reference: Kirshblum, S. C., Waring, W., Biering-Sorensen, F., Burns, S. P., Johansen, M., Schmidt-Read, M., . . . Krassioukov, A. (2011). *Reference for the 2011 revision of the International Standards for Neurological Classification of Spinal Cord Injury. Journal of Spinal Cord Medicine, 34(6), 547-554.*

Appendix 1C: Functional Independence Measure

Functional Independence Measure (FIM)

- often considered the gold standard for assessing basic activities of daily living (ex. self care).
- consists of two subscales, motor and socio-cognitive.

ICF Domain:

Activity – Subcategory: Self-Care

Number of Items:

18

Instructions for Administration and Scoring:

Administration:

- clinician-administered; completed by observation of performance.
- The motor subscale includes 13 items: eating, grooming bathing, dressing upper extremity, dressing lower extremity, bowel management, bladder management, transfers to bed, chair or wheelchair, transfer to tub, toilet and shower, walking or wheelchair propulsion and stair climbing.
- The socio-cognitive subscale includes 5 items: comprehension, expression, social interaction, problem solving and memory.
- administration is typically conducted by interdisciplinary team members
- Administration usually takes **approximately 45 minutes**, though short and phone versions also exist and may take more/less time to administer.

Equipment: Items that the patient uses to carry out activities of daily living.

Scoring:

- Each item is scored on a 7 point ordinal scale ranging from 1 (total dependence) to a score of 7 (total independence).
- The scoring considers the use of adaptive equipment and/or the extent of personal assistance or supervision required to complete the task. If assistive equipment (ex. raised toilet seat) is used, the individual cannot achieve a score of 7 on the item.
- FIM motor, cognitive and/or total scores can be derived by summing items.
- Total FIM scores range from 18 (totally dependent) to 126 (totally independent); motor scores range from 13 (total dependence) to 91 (total independence); and cognitive scores range from 5 (total dependence) to 35 (total independence).

Interpretability:

MCID: not established for the SCI population, but for an acute stroke sample, MCID = 22 points (for FIM Total score), 17 points (for FIM-Motor subscale) and 3 points (for FIM-Cognitive subscale). [Beninato et al. 2006, "Determination of the minimal clinically important difference in the FIM instrument in patients with stroke", n=113]

SEM: not established

MDC: not established

- Higher scores reflect fewer care hours required upon discharge.
- No normative data for the SCI population has been established.
- Published data for the SCI population is available for comparison for the FIM (see Interpretability section of the respective Study Details sheets).

Languages:

English, German, Italian, Spanish, Swedish, Finnish, Portuguese, Afrikaans, Turkish and French.

Training Required:

Certification for FIM administration is required.

Availability:

Can be purchased through http://www.udsmr.org/WebModules/FIM/Fim_About.aspx

Clinical Considerations:

- Though it is the best researched measure of basic function, it may not be sensitive to the subtle important changes in function for SCI individuals.
- The FIM is not SCI specific. It has limitations in sensitivity to component abilities within tasks for people with SCI. There is a ceiling effect with the socio-cognitive subscale for individuals with and it does not measure the social, psychological, or vocational impact of disability experienced by those living with SCI.
- Punitive scoring for individuals who use assistive technology occurs although these individuals may be independent
- Typically requires individuals from a number of different backgrounds (nurse, physical therapy, occupational therapy) to complete

Measurement Property Summary:

of studies reporting psychometric properties: 27

Reliability:

- Overall reliability is **excellent** for the total FIM (ICC=0.96), the FIM motor scale (ICC=0.90-0.96) and the FIM cognitive scale (ICC=0.91-0.98).
- Test-retest reliability of the FIM is **excellent** (ICC=0.89).

[Segal et al. 1993, Kucukdeveci et al. 2001, Lundgren-Nilsson et al. 2006, Morganti et al. 2005, Hall et al. 1999, Hamilton 1994, Dodds 1993, Nilsson 2005, Hamilton 1999, Heinemann et al. 1997]

Validity:

- Correlation of the FIM is **excellent** with the:
 - Quadriplegia Index of Function (Spearman's $\rho = 0.97$)
 - Quadriplegia Index of Function – Modified (Spearman's $\rho = 0.93$)
 - Upper Extremity Motor Score (Spearman's $\rho = 0.84$)

- Rivermead Mobility Index (Spearman's $\rho = 0.9$)
- Barthel Index (Spearman's $\rho = 0.7$)
- Spinal Cord Independence Measure (Spearman's $\rho = 0.8$)
- Walking Index for Spinal Cord Injury (Spearman's $\rho = 0.70-0.77$)
- Berg Balance Scale (Spearman's $\rho = 0.72-0.77$)
- American Spinal Injury Association (ASIA) motor score (Spearman's $\rho = 0.91$)
- Correlation of the FIM is **adequate** with the:
 - ASIA light touch (Spearman's $\rho = 0.58$)
 - ASIA pinprick (Spearman's $\rho = 0.55$)
 - 50-Foot Walking Speed Test (Spearman's $\rho = 0.57$).

[Marino et al. 1993, Yavuz et al. 1998, Dijkers et al. 1999, Beninato et al. 2004, Kucukdeveci et al. 2011, Dijkers 1999, Donnelly et al. 2004, Ditunno et al. 2007, Middleton et al. 2006, Itzkovich et al. 2007, Lawton et al. 2006, Morganti et al. 2005, Marino 2004, Heinemann 1997, Graves 2005, Dodds 1993, Nilsson 2005, Hamilton 1999, Marino 1998, Mulcahey et al. 2004, Anderson et al. 2011]

Responsiveness:

- Significant improvements in FIM score were detected between admission and discharge FIM scores (effect size for total FIM = 1.36).

[Middleton et al. 2006, Spooren et al. 2006, Dodds et al. 1993, Anderson et al. 2011]

Floor/ceiling effect:

- Ceiling effects were reported on FIM-cognition items.
- For bed transfer, toilet transfer and bath transfer, a ceiling effect was detected in the paraplegia group and a floor effect was detected in the tetraplegic group.

[Davidoff 1990, Middleton et al. 2006, Hall et al. 1999]

Reviewer:

Dr. William Miller, Christie Chan

Date Last Updated:

Feb 1, 2013

Appendix 1D: EQ-5D Scale



Health Questionnaire

English version for the UK

Sample

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

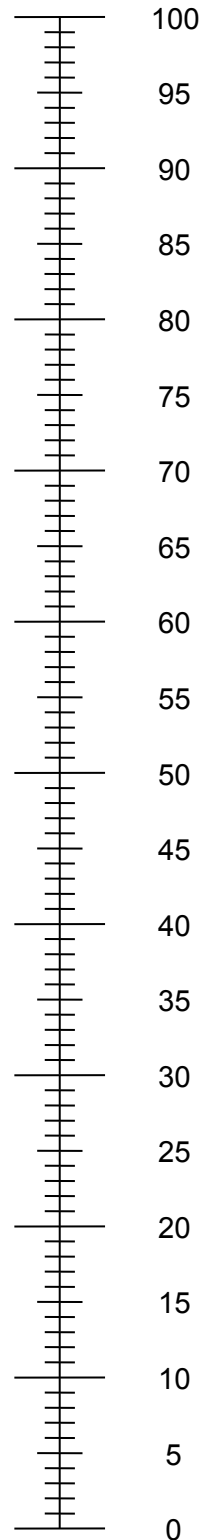
ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine



The worst health
you can imagine

Appendix 1E: Clinical Assessments used in Clinical Case Series

The Visual Analogue Pain Scale (VAS) was used in its format of the **Faces Rating Scale (FRS)**. The VAS has been established as reliable and valid in clinical research by a number of authors (Hawker, Mian, Kendzerska, & French, 2011; McCormack, Horne, & Sheather, 1988). The FRS is in the format of six facial expressions suggesting various pain intensities. The patient was asked to choose the face that best describes how they feel. The far left face indicates ‘No hurt’ and the far right face indicates ‘Hurts worst’. The number below the face chosen was documented.



Range of motion (ROM) is a description of how much movement exists at a joint. Joint ROM can be assessed through a variety of methods, but in this trial ROM was measured using a universal goniometer, using the protocol described by Clarkson (2000). A goniometer is a device used to measure joint angles or range-of-motion (in degrees) of joints for either active or passive joint range. Although inter-rater reliability of goniometric measures of ROM has been found to be poor (van Trijffel, van de Pol, Oostendorp, & Lucas, 2010), intra-rater reliability has been found to be good in the clinical setting in both the hip and the knee joints (Boone et al., 1978; Holm et al., 2000; Rothstein, Miller, & Roettger, 1983), hence there was one independent assessor. The mean of three trials of each movement was used in the analysis (Gajdosik, & Bohannon, 1987)



Functional Reach (FR) is a clinically accessible measure of balance and has been found to be reliable, precise and a reasonable clinical approximation of the margin of stability (Duncan, Weiner, Chandler, & Studenski, 1990).

The patient is instructed to next to, but not touching, a wall and position the arm that is closer to the wall at 90 degrees of shoulder flexion with a closed fist.

The assessor records the starting position at the 3rd metacarpal head on the yardstick.

Instruct the patient to “Reach as far as you can forward without taking a step.”

The location of the 3rd metacarpal is recorded.

Scores are determined by assessing the difference between the start and end position is the reach distance, usually measured in centimetres. Three trials were performed and the average of the last two was noted. FR was used for those patients who were able to stand.



Modified Functional Reach (MFR) has also been shown to be a reliable measure of sitting balance for those clients unable to stand (Katz-Leurer, Fisher, Neeb, Schwartz, & Carmeli, 2009).

This test is performed with a levelled yardstick that has been mounted on the wall at the height of the patient's acromion level while sitting in a chair.

Hips, knees and ankles are positioned at 90 degree of flexion, with feet flat on the floor.

The initial reach is measured with the patient sitting against the back of the chair with the upper-extremity flexed to 90 degrees; measure was taken from the distal end of the third metacarpal along the yardstick.

Instructions should include leaning as far as possible forward without rotation and without touching the wall. The distance in centimetres covered will be recorded. Three trials were performed and the average of the last two was noted.



Temporal and Distance Measures (Velocity, Stride Length, Cadence) was measured using the 10 metre walk test and the 6 –minute walk test (6MWT). These tests are simple, quick and can be used with minimal equipment. They have been shown to be reliable and valid in monitoring improvements in TBI patient groups(Rossier & Wade, 2001; van Hedel, Wirz, & Dietz, 2005; van Loo, Moseley, Bosman, De Bie, & Hassett, 2004; Wall, Devlin, Khirchof, & Lackey, 2000).

Test procedure for 10m walk:

The patient stands at one end of the walkway, and uses their regular walking aid. Given the following instructions; “Walk at your comfortable walking speed to the other end of this walkway, without stopping or talking until you reach the other end”. The therapist walks beside the patient, starts the stopwatch and commences counting strides as the first foot crosses the two metre mark of the walkway. The stopwatch and counting stop as the patient’s first foot crosses the two metre mark at the end of the walkway. Data collected over the central (10 meter section only).

Test procedure for 6MWT:

The patient is positioned at the start of the walking track and given the standardised instructions; “Walk as quickly as you can for six minutes to cover as much ground as possible. You may stop if you have to, but continue again as soon as you are able”. On the instruction to start the therapist starts the stopwatch. At six minutes the patient is instructed to stop and the distance travelled is calculated. The therapist should avoid giving motivational feedback. If the patient needs to stop, rest periods are included in the measurement time.

These tests were performed by the ambulant patients only; for the “10 metre walk” we have measured time over 10 metres and the number of steps; velocity and cadence was evaluated from these measures. Cadence is the number of steps per minute.

The Functional Independence Measure (FIM) assesses physical and cognitive disability. It consists of two subscales, motor and socio-cognitive with 18 assessable items in total. The tool is completed by observation of performance. The motor subscale, which is the portion to be assessed in this trial includes 13 items: eating, grooming bathing, dressing upper extremity, dressing lower extremity, bowel management, bladder management, transfers to bed, chair or wheelchair, transfer to tub, toilet and shower, walking or wheelchair propulsion and stair climbing. Each item is scored on a 7 point ordinal scale ranging from 1 (total dependence) to a score of 7 (total independence). **Motor** FIM scores range from 13 (total dependence) to 91 (total independence). Reliability and validity is well-established (Kidd et al., 1995). The FIM has been translated into 10 languages, including English and Hebrew, the languages to be used in this study. Certification for FIM administration is required and the independent assessor was certified in the motor component.

The European Quality Of Life –Dimensions questionnaire (EQ-5D) is a standardised generic instrument designed for describing and valuing health by providing a single summary index value representing the overall health-related quality of life of an individual by quantifying a preference for his or her health state. The EQ-5D instrument consists of a self-classifier/ descriptive system to describe the

respondent's own health in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Respondents can value their health in each dimension at three ordinal levels: no problems, some or moderate problems, and severe or extreme problems. The second measurement component of the EQ-5D is a 20 cm vertical Visual Analogue Scale (EQ VAS) to rate the respondent's own health. The third component of the EQ-5D is a questionnaire on the respondent's background including medical history. Recently, the EQ-5D was administered to a nationally representative sample in a large-scale study aiming to describe the current health status and the values of different health states of the Israeli population (Horowitz, Abadi-Korek, Shani, & Shemer, 2010). This study has been registered and permission obtained to use the EQ-5D from EuroQuol.org.

Plain X-ray - Neurogenic Heterotopic Ossification (NHO) becomes evident on plain radiography approximately 2 to 6 weeks after clinical diagnosis (Freed, Hahn, Menter, & Dillon, 1982; Orzel & Rudd, 1985). An X-ray view was set up for each patient and recorded so that it could be repeated. The view does not need to be a standard view; it is the patient's particular view that is important and reproducible. Measurements were made along co-ordinates - set up for that patient – e.g. the largest and shortest diameters. Plain X-ray was taken pre-intervention and six months post-intervention. All measurements are to be made along co-ordinates - set up for each patient – e.g. the largest and shortest diameters. Changes in the size of NHO were calculated by an expert radiologist (AL) using the Clearcanvas PACS system (*Clearcanvas Inc. 1920-439 University Avenue, Toronto ON M5G 1Y8*)

ClearCanvas RIS/PACS is an image management system whose intended use is to provide scalable DICOM compatible PACS solutions for hospitals and related institutions and sites, which will archive, distribute, retrieve and display images and data from all hospital modalities (such as CR, CT, DR, MR, and other devices) and information systems.

Serum alkaline phosphatase (SAP) levels have been reported to parallel the activity of ossification (Furman, et al., 1970). SAP levels start to rise about seven weeks before the first clinical signs of NHO become apparent, exceed normal levels one week later and reach peak levels three weeks after the first clinical signs (Orzel & Rudd, 1985).

Subsequently the SAP levels gradually decline to normal. The normative value for alkaline phosphatase (ALP) is 53 - 128 units per litre (U/L) in a 20 to 50 year-old man and 42 -98 U/L in a 20 to 50 year-old woman. Adults over 61 years have normative values of ALP of 51-153 U/L (Burtis, Ashwood, & Bruns, 2012; Collins, 2008). Serum alkaline phosphatase levels were taken at weeks 0, 10 and 22, to ensure that the NHO remained inactive.

Appendix 1F: Radiographic Assessment Methodology

The areas of soft tissue ossification were highly irregular and non-anatomical, therefore prominent points that were clearly visible on images from both early and late studies were selected. The diameter of the ossified lesion was measured at this point, (Measurement 1) and a measurement at right angles also taken (Measurement 2). If /or when the ossified mass was particularly irregular, more than one prominent point was chosen and a second diameter measurement taken (Measurement 3).

Equivalent measurements of AP and Lateral, on the Early and Late studies were compared.

It was noted that the radiographic technique between the early and late studies was slightly different;

Variations in exposure were compensated using the Window width/level tool in Clearcanvas PACS. Brightness and contrast were altered until adjacent normal bone was equivalent on the early and late studies.

Variation of magnification was estimated by comparing a measurement of the width of normal bone shaft at a standard point on each study. This was obtained by measuring from a recognisable normal structure (e.g. medial tibial plateau, tip of the medial femoral condyle, or weight bearing surface of the femoral head, depending upon the study) to a proximal area of normal bone 10 - 13 cm from the selected structure. The width of the bone shaft at this point was obtained on equivalent projections, AP, and Lateral, of the early study and compared to the similar image on the late study. Where a significant difference occurred this was used to correct for variations of magnification of the measurements of the lesions.

Qualitative changes between Early and Late studies were assessed by examination of the images after correction for exposure. The margins of the lesions were examined for changes in clarity or fragmentation. Any trabeculation within the ossified areas was assessed for increase or decrease in number and for changes in density of the trabeculae. Any new bone was assessed. Any loss of bone was noted.

(Note that by deliberately altering brightness and contrast to be equivalent actual osteoporotic changes occurring in the patient due, for example to immobility, could be obliterated. This may lead to error).

Appendix 2: Ethics Approvals

Appendix 2A: JCU External HREC Approval RAH Protocol Number 121124

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Appendix 2B: Royal Adelaide Hospital

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Appendix 2C: Townsville Hospital and Health Service

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Appendix 2D: Loewenstein Hospital Rehabilitation Center

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**Appendix 2E: Extension of Ethics Approval from Beit Loewenstein Hospital
until 13 September 2016**

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Appendix 2F: ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt

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Appendix 3: Permissions and Papers

Appendix 3A: Permissions

Permission for paper:

Reznik, J.E., Milanese, S., Golledge, J., Biros, E., Gordon, S.J., & Galea MP. (2013b) Extracorporeal shock wave therapy as a treatment for heterotopic ossification: A systematic review and meta-analysis of published data. *Physical Therapy Reviews* 18(4): 300-307.

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Permission for paper:

Reznik, J.E., Biros, E., Marshall, R., Jelbart, M., Milanese, S., Gordon, S.J., & Galea, M.P. (2014). Prevalence and risk-factors of neurogenic heterotopic ossification in traumatic spinal cord and traumatic brain injured patients admitted to specialised units in Australia. *Journal of Musculoskeletal and Neuronal Interactions*. 14(1), 19-28.

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Permission for paper:

Reznik, J.E., Biros E., Milanese S., Gordon SJ., Lamont AC., & Galea MP (2015). Prevalence of neurogenic heterotopic ossification in traumatic head and spinal injured patients admitted to a tertiary referral hospital in Australia. *HealthCare Manager* 34:1 (January-February 2015).

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Permission for paper:

Reznik, J.E., Gordon S.J., Barker R.N., Keren, O., Arama, Y., & Galea MP. (2013a) Extracorporeal shock wave therapy (ESWT) as a treatment for recurrent neurogenic heterotopic ossification (NHO) *Brain Injury* 27(2):242-7.

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Appendix 3B: Paper

**Reznik, J.E., Milanese, S., Golledge, J., Biro, E., Gordon, S.J., & Galea MP.
(2013b) Extracorporeal shock wave therapy as a treatment for heterotopic
ossification: A systematic review and meta-analysis of published data. Physical
Therapy Reviews 18(4): 300-307**

Systematic Review

Extracorporeal shock wave therapy as a treatment for heterotopic ossification

Jacqueline E. Reznik¹, Steve Milanese^{1,2}, Jonathon Golledge¹, Erik Biro¹, Susan Gordon¹, Mary P. Galea^{1,3}

¹James Cook University, Townsville, QLD, Australia, ²University of South Australia, Adelaide, Australia, ³The University of Melbourne, VIC, Australia

Background: Extracorporeal shock wave therapy (ESWT) is an intervention treatment in musculoskeletal conditions. Heterotopic ossification (HO) is a painful osseous condition of various origins, with the potential to cause significant incapacity.

Objectives: To summarize the published data and assess the effectiveness of ESWT as a therapeutic intervention for patients with HO.

Methods: A systematic search of the literature using Medline via Ovid, Scopus, CINAHL, and Web of Science databases. Reference lists of all articles found were also hand-searched. Articles were assessed using the Oxford Centre for Evidence Based Medicine (OCEBM) hierarchy of evidence and were critically appraised using the McMaster Critical Review Form for Quantitative Studies.

A meta-analysis of data from four independent case studies totaling 52 HO patients treated with ESWT was performed. Outcome was assessed by pain and range of motion (ROM) of hip and knee flexion, since this was the only recorded movement data in the studies. Data were analyzed with a fixed effects model.

Results: Only four articles met the inclusion criteria. Hierarchical evidence scores were low, but the articles scored well on the critical appraisal tool. ESWT led to an improvement in knee flexion by approximately 82% [95% confidence interval (CI): 66.58–96.87; $P < 0.001$] and hip flexion of ~10% (95% CI: 1.36–20.44; $P = 0.086$). Approximately 25% of relative improvement in ROM can be attributed to alleviation of pain after ESWT ($r^2 = 0.25$; $P = 0.496$).

Conclusion: ESWT may be associated with clinically significant improvement of ROM of lower extremities in patients with HO although larger studies are needed to confirm these findings.

Keywords: Extracorporeal shock-wave therapy, Heterotopic ossification, High energy shock wave therapy, Myositis ossificans

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Appendix 3C: Paper

Reznik, J.E., Biros, E., Marshall, R., Jelbart, M., Milanese, S., Gordon, S.J., & Galea, M.P. (2014). Prevalence and risk-factors of neurogenic heterotopic ossification in traumatic spinal cord and traumatic brain injured patients admitted to specialised units in Australia. *Journal of Musculoskeletal and Neuronal Interactions*. 14(1), 19-28.

Original Article

Prevalence and risk-factors of neurogenic heterotopic ossification in traumatic spinal cord and traumatic brain injured patients admitted to specialised units in Australia

J.E. Reznik¹, E. Biros², R. Marshall³, M. Jelbart⁴, S. Milanese^{1,5}, S. Gordon¹, M.P. Galea^{1,6}

¹Physiotherapy, James Cook University, Townsville, QLD 4811, Australia; ²Queensland Research Centre for Peripheral Vascular Disease, Townsville, QLD 4811; ³Amputee & Spinal Injury Rehabilitation Service, Hampstead Rehabilitation Centre/Royal Adelaide Hospital, Adelaide, S.A., Australia;

⁴Brain Injury Rehabilitation Service, Hampstead Rehabilitation Centre, Adelaide, S.A., Australia; ⁵Physiotherapy, University of South Australia, Adelaide, S.A., Australia; ⁶Department of Medicine, (Royal Melbourne Hospital) The University of Melbourne, VIC 3010, Australia

Abstract

Objectives: To identify the prevalence and risk factors in the development of Neurogenic Heterotopic Ossification (NHO) in traumatic brain and spinal cord injured patients admitted to specialised units. **Methods:** An audit protocol was used to gather all clinically relevant data, in specific patient groups, relating to the prevalence of NHO, and was statistically analysed to identify traumatic brain injury (TBI) and traumatic spinal cord injury (TSCI) patients at high risk of developing NHO. **Results:** 262 TBI and 151 TSCI patients were identified. NHO was diagnosed in 10 and 16 patients with TBI and TSCI, respectively; 18 clinically relevant characteristics were analysed for association with NHO in these patient groups. The only common variables associated with NHO in both neurological conditions were deep vein thrombosis and/or pulmonary emboli (DVT/PE). **Conclusions:** The prevalence of NHO in TBI patients is less than one-third of that found in TSCI patients, ~4% and 11%, respectively. This study also suggests that the risk factors associated with NHO in TBI patients are distinct from those identified as risk factors in TSCI patients.

Keywords: Brain Injury, Spinal Cord Injury, Traumatic, Neurogenic Heterotopic Ossification

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Appendix 3D: Abstract of Paper

**Reznik, J,E., Biros E., Milanese S., Gordon SJ., Lamont AC., & Galea MP (2015).
Prevalence of neurogenic heterotopic ossification in traumatic head and spinal
injured patients admitted to a tertiary referral hospital in Australia. *HealthCare
Manager* 34:1 (January-February 2015).**

Full paper text available at:

<http://researchonline.jcu.edu.au/31276/>

Prevalence of Neurogenic Heterotopic Ossification in Traumatic Head- and Spinal-Injured Patients Admitted to a Tertiary Referral Hospital in Australia

**Jacqueline E. Reznik, B App Sci (Physio); Erik Biros, PhD;
Steve Milanese, PhD; Susan Gordon, PhD; Anthony C. Lamont, MD;
Mary P. Galea, PhD**

A study was undertaken to investigate the prevalence of neurogenic heterotopic ossification (NHO) in patients with traumatic brain injury (TBI) or traumatic spinal cord injury (TSCI) admitted to non-specialized units. Methods consisted of a retrospective audit of patients, using the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM)* coding system, admitted to The Townsville Hospital with TBI/TSCI between July 1, 2006, and December 31, 2012. Fifty-eight patients with length of stay of 60 days or longer were admitted to The Townsville Hospital with TBI/TSCI over this period with mean age of 60 years (range, 31-87 years); 55 were TBI and 3 were TSCI patients. Three thousand one hundred fourteen TBI/TSCI patients with length of stay of less than 60 days and mean age of 43 years (range, 18-93 years) were also identified (2903 were TBI and 211 were TSCI patients). Overall, none had a diagnosis of NHO; 6 patients, identified by the *ICD-10-AM* codes, with a diagnosis of heterotopic ossification did not have an associated TBI/TSCI. Findings of 0% of NHO prevalence in TSCI/TBI patients admitted to the large tertiary referral hospital suggest that NHO may have been missed, possibly because of the TSCI/TBI *ICD-10-AM* codes, not being specifically designed for documentation of the TBI/TSCI complications. If NHO remains undiagnosed in nonspecialized units because of the method of coding, it may increase functional limitation in already compromised individuals. Key words: *brain injury, ICD-10 coding, neurogenic heterotopic ossification, spinal cord injury, traumatic*

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Author Affiliations: James Cook University, Townsville (Ms Reznik, Drs Biros, Gordon, Lamont, and Galea); University of South Australia (Dr Milanese); The Townsville Hospital (Dr Lamont); and The University of Melbourne (Dr Galea), Australia.

The authors have no conflicts of interest.

Correspondence: Jacqueline E. Reznik, B App Sci (Physio), POB 165, James Cook University, Townsville, QLD 4811, Australia (jackie.reznik@jcu.edu.au).

DOI: 10.1097/HCM.0000000000000044

Appendix 3E: Paper

**Reznik, J.E., Gordon S.J., Barker R.N., Keren, O., Arama, Y., & Galea MP.
(2013a) Extracorporeal shock wave therapy (ESWT) as a treatment for recurrent
neurogenic heterotopic ossification (NHO) Brain Injury 27(2):242-7.**

CASE STUDY

Extracorporeal Shock Wave Therapy (ESWT) as a treatment for recurrent Neurogenic Heterotopic Ossification (NHO)

JACQUELINE E. REZNIK¹, SUSAN J. GORDON¹, RUTH N. BARKER¹, OFER KEREN², YUVAL ARAMA³, & MARY P. GALEA^{1,4}

¹School of Public Health, Tropical Medicine and Rehabilitation Sciences, James Cook University, Queensland, Australia, ²Head Injury Department, Sheba Medical Center, Ramat Gan, Israel, ³Department of Orthopaedics, Assaf Harofe Medical Center, Tzrifin, Israel, and ⁴Rehabilitation Sciences Research Centre, The University of Melbourne, Melbourne, Australia

(Received 19 September 2011; accepted 15 August 2012)

Abstract

Primary objective: To describe the effects of extracorporeal shock wave therapy (ESWT) on neurogenic heterotopic ossification (NHO).

Research design: A single case study was considered the most appropriate methodology in this situation.

Methods and procedures: The subject was a 43 year old female 10 years post-traumatic brain injury with recurring NHO around the hip joint. Baseline assessments of pain using a 10-point VAS, range of motion of the hip using a goniometer and walking ability (number of steps over a standard distance) were conducted. Four applications of ESWT using a MinispecTM Extracorporeal Shock Wave Lithotripsy machine (Medispec Int. USA) administered over 6 weeks to the anterolateral aspect of the right hip. Follow-up assessments were conducted weekly over the period of intervention and then monthly for 5 months.

Main outcomes and results: Immediately following treatment, pain was reduced to 0 on the VAS scale; hip range of motion increased and the number of steps over a standard distance reduced, indicating increased step length. At 5-month follow-up, without further ESWT intervention, these results were maintained.

Conclusion: This case study suggests that ESWT may be a non-invasive, low risk intervention for the management of NHO.

Keywords: Brain injury, traumatic brain injury (TBI), neurogenic heterotopic ossification (NHO), extracorporeal shock wave therapy (ESWT)

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Appendix 4: CRF Case Report Form

Intervention copy

Effect of Extracorporeal Shock Wave
Therapy on Chronic Neurogenic
Heterotopic Ossification
(ESWT for NHO)

Case Report Form (CRF)

Beit Loewenstein Rehabilitation Centre

Pages 2-9: To be completed by Independent Assessor and Medical Officer

Pages 10-16: To be completed by Principal Investigator

Screening

Patient ID: _____

Visit date: -- --/ -- --/ -- -- (d/m/y)

Inclusion Criteria

Participant must:

- | | | |
|--|------------------------------|-----------------------------|
| 1. <u>Be over 18 years of age</u> | ☐ Yes | ☐ No |
| 2. Be brain injured with a diagnosis of NHO around the hip and/ or knee for a period of greater than <u>one year</u> | ☐ Yes | ☐ No |
| 3. Be able, or have a legal guardian who is willing, to provide <u>consent after both oral and written information</u> | ☐ Yes | ☐ No |

NOTE: All inclusion criteria must be answered YES to be included in study.

Exclusion Criteria

Participant must not:

- | | | |
|---|------------------------------|-----------------------------|
| 1. <u>Be pregnant</u> | ☐ Yes | ☐ No |
| 2. Have a diagnosis of rheumatoid arthritis, ankylosing spondylitis or acute femoral/pelvic fractures | ☐ Yes | ☐ No |
| 3. Have evidence of active bone remodelling on bone scan | ☐ Yes | ☐ No |

NOTE: All exclusion criteria must be answered NO to be included in study.

Did the participant meet the eligibility requirements for this study?
No ☐ Yes ☐

Investigator Signature: _____

-- --/ -- --/ -- -- (d/m/y)

Screening Demographics

Patient ID:

Visit date: -- --/ -- --/ -- -- (d/m/y)

- Gender: ☐ Female ☐ Male
- Date of Birth: / /
- Ethnicity (with which you MOST CLOSELY identify):
- Language (with which you MOST CLOSELY identify):
- Current occupation: ☐ Paid employed ☐ Self-employed ☐ Non-paid work
☐ Student ☐ Keeping house ☐ Retired
☐ unemployed ☐ other
- TBI participants: Baseline GCS PTA
- Height (cm)
- Weight (kg)

Date Informed Consent Signed:

 / /

d d m m y y y y

Investigator Signature: _____

 / /

d d m m y y y y

Screening

Medical History

Patient ID: _____

Visit date: -- --/ -- --/ -- -- (d/m/y)

Does the participant have a medical or surgical history, current or resolved, of any of the following?

MEDICAL HISTORY	Yes /No	Unknown	If Yes, Explain	Current / Resolved
1. Head, Eye, Ear, Nose, Throat	☐ Yes ☐ No	☐		☐ Current ☐ Resolved
2. Respiratory	☐ Yes ☐ No	☐		☐ Current ☐ Resolved
3. Cardiovascular	☐ Yes ☐ No	☐		☐ Current ☐ Resolved
4. Gastrointestinal	☐ Yes ☐ No	☐		☐ Current ☐ Resolved
5. Genitourinary	☐ Yes ☐ No	☐		☐ Current ☐ Resolved
6. Musculoskeletal	☐ Yes ☐ No	☐		☐ Current ☐ Resolved
7. Neurological	☐ Yes ☐ No	☐		☐ Current ☐ Resolved
8. Endocrine-Metabolic	☐ Yes ☐ No	☐		☐ Current ☐ Resolved
9. Blood/Lymphatic	☐ Yes ☐ No	☐		☐ Current ☐ Resolved
10. Dermatologic	☐ Yes ☐ No	☐		☐ Current ☐ Resolved
11. Psychiatric	☐ Yes ☐ No	☐		☐ Current ☐ Resolved
12. Allergy	☐ Yes ☐ No	☐		☐ Current ☐ Resolved
13. Other, specify: _____	☐ Yes ☐ No	☐		☐ Current ☐ Resolved

MO Signature: _____ _ _ / _ _ / _ _ _ _
d d / m m / y y y y

Laboratory Assessments

Patient ID:

Visit date: -- --/ -- --/ -- -- (d/m/y)

Date	Normative values: Adults 25-60: 33-131IU/L Adults > 61 : 51-153 IU/L	IU/L
	Screening/Baseline serum alkaline phosphatase (SAP) level	
	During-intervention SAP level (10/52)	
	Post-intervention (22/52)	

Report attached

Yes/No

MO Signature: _____ / /

Prior and Concomitant Medications and/or Therapy

Patient ID: _____

Visit date: -- --/ -- --/ -- -- (d/m/y)

Were any concomitant medications/therapy taken by the participant within the last two weeks?

☐ Yes (If so, record below.)

☐ No

Medication	Therapy	Indication	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)	Ongoing
1.					☐
2.					☐
3.					☐
4.					☐
5.					☐

MO Signature: _____ / /

Enrollment Form

Medical History

Patient ID: _____

Visit date: -- --/ -- --/ -- -- (d/m/y)

Is the participant eligible for the study based on inclusion and exclusion criteria?

☐ Yes

☐ No (If no, leave the rest of the form blank.)

If yes:

4. Date enrolled (met all eligibility criteria):

 / /
d d m m y y y y

or

5. If eligible and not enrolled, indicate reason:*

☐ Failed to return ☐ Declined participation ☐ Other (specify): _____

*Optional

MO Signature: _____

 / /
d d m m y y y y

Physiotherapy Assessment

Patient ID:

Visit date: -- --/ -- --/ -- -- (d/m/y)

Variable		Score		
Faces Rating Scale for pain				
Recording sheet attached				Yes/No
Temporal and distance measures of gait.	1.Cadence <i>(steps per minute)</i>	Trial 1	Trial 2	Trial 3
	2. Velocity (m/min)	Trial 1	Trial 2	Trial 3
	3. Stride length (m)	Trial 1	Trial 2	Trial 3
6 minute walk test <i>(Distance walked at comfortable speed)</i>		Trial 1	Trial 2	Trial 3

Range of Motion (in degrees) One practice and three trials for each movement		(R)H/K		(R)H/K		(R)H/K		(L)H/K		(L)H/K		(L)H/K	
		1		2		3		1		2		3	
Hip	Knee	H	K	H	K	H	K	H	K	H	K	H	K
Flexion	Flexion												
Extension	Extension												
Abduction													
Adduction													
Internal rotation													
External rotation													

Functional reach or Modified Functional Reach (in cms) One practice and three trials	Trial 1	Trial 2	Trial 3
EQ-5D Questionnaire – attached Baseline, Post-intervention/3mnths, 6mnths	Yes/No		
FIM Questionnaire – attached Baseline, immediate, three and six months post-intervention	Yes/No		
X-ray (Attached) Baseline and six months post –intervention only	Yes/No		

Physiotherapy Assessment

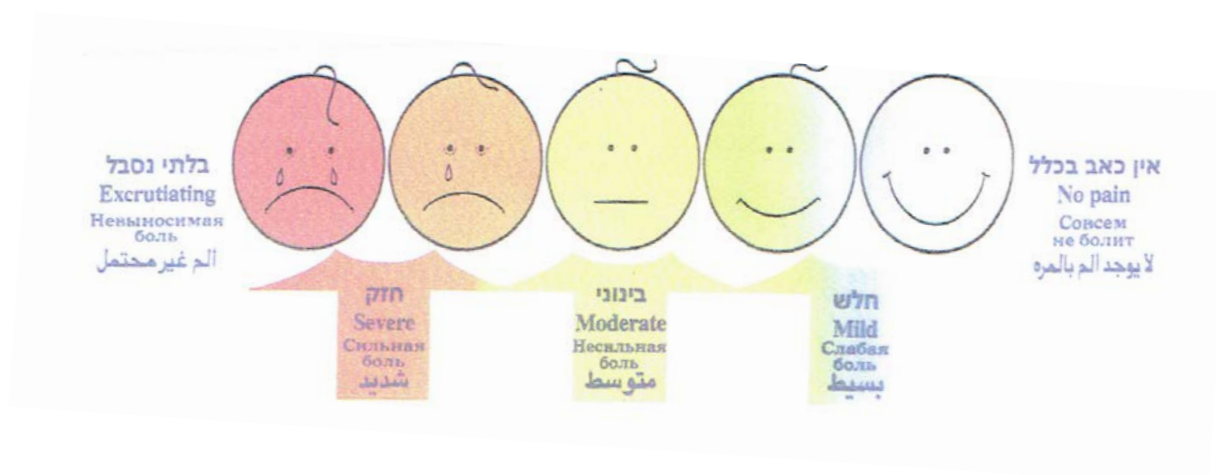
Patient ID:

Visit date: -- --/ -- --/ -- -- (d/m/y)

Faces Rating scale:

Adults who have difficulty using the numbers on the visual/numerical rating scales can be assisted with the use of the six facial expressions suggesting various pain intensities. Ask the patient to choose the face that best describes how they feel. The far left face indicates 'No hurt' and the far right face indicates 'Hurts worst'.

Participant will be shown the ruler as outlined below.



Indicate on the Wong Baker Face Scale below where the participant pointed to.

Document number below the face chosen.



Physiotherapy Assessment

Patient ID:

Visit date: -- --/ -- --/ -- -- (d/m/y)

Temporal and Distance Measures (Velocity, Stride Length, Cadence):

Test procedure:

The patient stands at one end of the walkway, and uses their regular walking aid. Given the following instructions; "Walk at your comfortable walking speed to the other end of this walkway, without stopping or talking until you reach the other end". The therapist walks beside the patient, starts the stopwatch and commences counting strides as the first foot crosses the two metre mark of the walkway. The stopwatch and counting stop as the patient's first foot crosses the two metre mark at the end of the walkway. Data collected over the central (10 meter section only).

Six Minute Walk Test:

Test procedure:

The patient is positioned at the start of the walking track and given the standardized instructions; "Walk as quickly as you can for six minutes to cover as much ground as possible. You may stop if you have to, but continue again as soon as you are able". On the instruction to start the therapist starts the stopwatch. At six minutes the patient is instructed to stop and the distance travelled is calculated. The therapist should avoid giving motivational feedback. If the patient needs to stop, rest periods are included in the measurement time.

Physiotherapy Assessment

Patient ID: _____

Visit date: -- --/ -- --/ -- -- (d/m/y)

Observations:

- How have you been feeling since the last assessment?

- Note skin colour over hip/knee

- Any adverse events since last assessment?

Adverse effect – checklist.

- Erythema
- Swelling
- Skin Irritation
- Pain – note site
- Other (describe) _____

Assessors Signature: _____

_____/_____/_____
d d m m y y y y

Intervention Form

Patient ID: _____

Visit date: -- --/ -- --/ -- -- (d/m/y)

VAS Pre-treatment:

☐

Treatment number	No. of 1 cm ² areas to be treated	No. of shocks per area ≤500	Energy Flux density	Total no. of shocks given per treatment ≤3000

Treatment #2 onwards

Observations:

- How have you been feeling since the last assessment?

- Note skin colour over hip/knee

- Any adverse events since last assessment?

Adverse effect – checklist.

- Erythema
- Skin Irritation
- Pain – note site
- Other (describe) _____

PI Signature: _____

 / /
d d m m y y y y

Adverse Event Form

Patient ID:

Visit date: -- --/ -- --/ -- -- (d/m/y)

Has the participant had any adverse events (AE) during this study? ☐ Yes ☐ No (if yes, please list all adverse events below.)

Severity	Study Intervention Relationship	Action Taken Regarding Study Intervention	Outcome of AE	Expected	Serious
1 = Mild 2 = Moderate 3 = Severe	1 = Definitely related 2 = Possibly related 3 = Not related	1 = None 2 = Discontinued permanently 3 = Discontinued temporarily 4 = Reduced dose 5 = Increased dose 6 = Delayed dose	1 = Resolved, no sequel 2 = AE still present, no treatment 3 = AE still present, being treated 4 = Residual effects present, not treated 5 = Residual effects present, treated 6 = Death 7 = Unknown	1 = Yes 2 = No	1 = Yes 2 = No (if yes, complete SAE form)

Adverse Event	Start Date	Stop Date	Severity	Relationship to Study Treatment	Action Taken	Outcome of AE	Expected	Serious Adverse Event	Initials
1.									
2.									
3.									
4.									

Serious Adverse Event (SAE) Report Form

Patient ID: _____

Visit date: -- --/ -- --/ -- -- (d/m/y)

1. SAE onset date: __ __ / __ __ / __ __ __ __
 d d m m y y y y

2. SAE stop date: __ __ / __ __ / __ __ __ __
 d d m m y y y y

3. Location of serious adverse event: _____

4. Was this an unexpected adverse event? ☐ Yes ☐ No

5. Brief description of participants with no personal identifiers:

Sex: ☐ F ☐ M Age: ____

Diagnosis for study participation: _____

6. Brief description of the nature of the serious adverse event (attach description if more space is needed):

7. Category of the serious adverse event:

☐ Date of death __ / __ / __
 (dd/mm/yyyy)

☐ Congenital anomaly/birth defect

☐ Life threatening

☐ Required intervention to prevent permanent impairment

☐ Hospitalization – initial or prolonged

☐ Other:

☐ Disability/incapacity

8. Intervention type:

☐ Medication or nutritional supplement (specify): _____

☐ Device (specify): _____

☐ Surgery (specify): _____

☐ Behavioral/lifestyle (specify): _____

9. Relationship of event to intervention:

☐ Unrelated (clearly not related to the intervention)

☐ Possible (may be related to intervention)

☐ Definite (clearly related to intervention)

10. Was study intervention discontinued due to event? ☐ Yes ☐ No

11. What medications or other steps were taken to treat the serious adverse event?

12. List any relevant tests, laboratory data, and history, including preexisting medical conditions:

13. Type of report:

☐ Initial

☐ Follow up

☐ Final

Signature of Principal Investigator: _____ Date: _____

Protocol Deviations Log

Patient ID	Deviation Category*	Deviation Code**	Date Deviation Occurred (dd/mm/yyyy)	Date IRB Notified (if applicable)	Principal Investigator's Signature	Date Signed (dd/mm/yyyy)

***DEVIATION CATEGORIES**

- A. Safety
- B. Informed consent
- C. Eligibility
- D. Protocol implementation
- E. Other, specify in log

****DEVIATION CODES: Numbers listed by the sample protocol deviations**

Safety (Category A)

- 1. Not reporting an SAE within 24 hours
- 2. Laboratory tests not done
- 3. AE/SAE is not reported to IRB
- 4. Other, specify in log

Informed consent (Category B)

- 5. Failure to obtain informed consent
- 6. Consent form used was not current IRB-approved version
- 7. Consent form does not include updates or information required by IRB
- 8. Consent form missing
- 9. Consent form not signed and dated by participant
- 10. Consent form does not contain all required signatures
- 11. Other, specify in log

Eligibility (Category C)

- 12. Participant did not meet eligibility criterion
- 13. Randomization of an ineligible participant
- 14. Participant randomized prior to completing baseline assessment, etc.
- 15. Randomization and/or treatment of participant prior to IRB approval of protocol
- 16. Other, specify in log

Protocol implementation (Category D)

- 17. Failure to keep IRB approval up to date
- 18. Participant receives wrong treatment
- 19. Participant seen outside visit window
- 20. Use of unallowable concomitant treatments
- 21. Prescribed dosing outside protocol guidelines
- 22. Missed assessment
- 23. Missed visit
- 24. Other, specify in log

Study Completion

Patient ID: _____

Visit date: -- --/ -- --/ -- -- (d/m/y)

1. Date of final study visit: $\frac{\text{d}}{\text{d}} / \frac{\text{m}}{\text{m}} / \frac{\text{y}}{\text{y}} \frac{\text{y}}{\text{y}} \frac{\text{y}}{\text{y}}$

2. Date of last-known study intervention: $\frac{\text{d}}{\text{d}} / \frac{\text{m}}{\text{m}} / \frac{\text{y}}{\text{y}} \frac{\text{y}}{\text{y}} \frac{\text{y}}{\text{y}}$

3. Primary reason for terminating participation in the study:

☐ Completed study

☐ Participant was determined after enrollment to be ineligible (provide comments):

☐ Participant withdrew consent

☐ In the principal investigator's opinion, it was not in the participant's best interest to continue (provide comments): _____

☐ Adverse event (If checked, complete the AE form.)

☐ Death

☐ Lost to follow-up

☐ Other (specify): _____

☐ Unknown

Comments:

PI Signature: _____

Date: _____

Appendix 5: Minispec Brochure



Minispec

Extracorporeal Shock Wave Therapy (ESWT)

The Minispec™ is Medispec's new generation system for the applications of non-invasive shock wave therapy in Orthopedics, Sports Medicine and Traumatology.

- High Success Rate
- Large Therapy Zone
- Non-invasive Extracorporeal Shockwave Therapy (ESWT)
- No need for Anesthesia
- Imaging not required



Minispec

Improved Performance and Clinical Results

A new High Technology Power Supply (SSPS) provides uniform shock waves that increase treatment efficiency.

New Ergonomic Design to Maximize Patient's Comfort

Ergonomic design provides patient comfort and improves accessibility - Patient comfortably seats during entire treatment.

Simplified Maintenance & Troubleshooting

All parts are easily accessible for routine maintenance (including external water filter) and can be changed within seconds.

Innovative Concept Reduces Imaging Requirements

Highly Effective system that reduces the need for imaging. In addition, patients no longer have to worry about exposure to radiation.

Compact & User-Friendly Design

System is more compact and can easily be stored in a small space when not in use.



Technical Specifications

Main Unit

Weight: 50 Kgs.

Dimensions: 580mm (L) x 220mm (W) x 580mm (H)

Energy Level: Adjustable from 1 to 7

Frequency: 96-160 ppm

Power Supply: 115 / 230V; single phase 50/60Hz; 10/5 A

Shockwave Applicator (MR-1)

Weight: 950g.

Dimensions: 92mm (diameter), 90mm (length)

Shock Wave Source: Electrohydraulic

Life Span: 50,000 shocks

Safety Classification: Class II, Type B



* Data subject to change without notice



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