REDUCTION OF POST-SURGICAL PERICARDIAL ADHESIONS USING A PIG MODEL

Thesis submitted by
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Master of Medicine
in the School of Veterinary and Biomedical Sciences
and School of Medicine
James Cook University
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ABSTRACT

The aim of this study was to reduce pericardial adhesions after open-heart surgery thus enabling re-sternotomies to be much safer and less time consuming for the surgical team. A pig model was developed to test the effects of non-steroidal anti-inflammatory drugs (NSAIDs) and a barrier method in reducing post-surgical pericardial adhesions. Four groups (11 per group) of pigs 8-12 weeks of age were used. Group one was the control group, Group two received indomethacin, Group three received rofecoxib (also a NSAID) and a polyethyleneglycol (Co-Seal) was applied to the pericardium as a barrier in Group four.

After performing a median sternotomy, an adhesion induction model was applied to maximize inflammation in the pericardium. This included abrasion of the heart surface, leaving blood in the pericardium and drying of tissues. The chest was then closed. In Group four, Co-Seal was sprayed on the heart before closure. Post-operatively, Groups two and three received indomethacin and rofecoxib respectively for five days. Plasma markers of inflammation were assessed on days 2, 5 and 10 post-operative. In each group, eight animals were re-opened after 12 weeks and three after 25 weeks to assess adhesions according to adhesion assessment scales. Tissue samples were collected for histopathological examination looking mainly at epicardial and adhesive tissue thickness.

It was observed in this study that adhesions were changed from dense to thin and more easily separable, requiring more blunt rather than sharp dissection. This was seen mainly in Group two, followed by Group four. In Group three, the changes were less in terms of amount of adhesions and tenacity change as compared to the changes in Groups two and four. Comparison was with Group one, which had the densest adhesions.

Adhesive tissue and epicardial thickness was measured. Epicardium was thinnest in Group two. Post-operative inflammatory markers, specifically PGE2 and TXB2 were inhibited mainly in Group two. Less inhibition of these markers was seen in Group three and nearly no inhibition was seen in Groups one and four. The more general
markers used (WCC, ESR and CRP) did not fully show the expected changes in the four groups. The adhesion induction model formulated in this study was successful and may be used in similar future projects.

In conclusion, this model, applied clinically, will reduce adhesions in the pericardium and retrosternal areas after surgery, rendering re-openings safer and less time consuming. Indomethacin has proven to be the best choice to achieve this following a relatively easy and short protocol of administration. The idea of giving patients indomethacin for five days only to achieve significant reduction in adhesion formation after surgery would be attractive to many surgical groups around the world as the short period of administration would minimize any side effects associated with this drug.

Significant reduction in adhesions was also seen following the application of Co-Seal. The attraction here would be the ease of use and the non-pharmacological effects of this barrier method. Rofecoxib was not as effective as indomethacin and Co-seal in adhesion reduction. Future studies in this pig model should examine the extent of adhesion formation following the combined use of indomethacin and Co-Seal.
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### ABBREVIATIONS

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<tr>
<td>AA</td>
<td>Arachidonic acid</td>
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<tr>
<td>AMP</td>
<td>Adenosine monophosphate</td>
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<td>ANOVA</td>
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<td>APS</td>
<td>Adhesion percentage scale</td>
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<td>APTT</td>
<td>Activated partial thromboplastin time</td>
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<td>ASD</td>
<td>Atrial septal defect</td>
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<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
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<td>ATTS</td>
<td>Adhesive tissue tenacity scale</td>
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<td>CAG</td>
<td>Coronary artery grafting</td>
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<td>Camp</td>
<td>3’, 5’-adenosine monophosphate</td>
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<td>COX</td>
<td>Cyclooxygenase</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<td>DAG</td>
<td>Diacylglycerol</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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<td>EDTA</td>
<td>Ethylene diamine tetra acetic acid</td>
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<td>ELAM-1</td>
<td>Endothelial-leukocyte adhesion molecule-1</td>
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<td>ESR</td>
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<td>IP3</td>
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<td>LFA</td>
<td>Lymphocyte function-associated antigen</td>
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LTA4  Leukotriene A4
LTD4  Leukotriene D4
LTE4  Leukotriene E4
MANOVA  Multivariate analysis of variance
MRNA  Messenger ribonucleic acid
N/D  Not detectable
NSAIDs  Non-steroidal anti-inflammatory drugs
NSW  New South Wales
NZ  New Zealand
PEG  Polyethyleneglycol
PGD2  Prostaglandin D2
PGE1  Prostaglandin E1
PGE2  Prostaglandin E2
PGF1  Prostaglandin F1
PGF2  Prostaglandin F2
PGI2  Prostaglandin I2
PIP2  Phosphatidylinositol-4, 5-biphosphate
PMN  Polymorphonuclear
PT  Prothrombin time
QLD  Queensland
SEM  Standard error of mean
SRS-As  Slow-reacting substances of anaphylaxis
TNF  Tumor necrosis factor
TPA  Tissue plasminogen activator
TxA2  Thromboxane A2
TxB2  Thromboxane B2
VIC  Victoria
VSD  Ventricular septal defect
WA  Western Australia
WBC  White blood cells
WCC  White Cell Count
5-LO  5-lipoxygenase