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Efficacy of Prednisolone for Bell Palsy in Children: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial

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ABSTRACT

Background and Objective

Corticosteroids are used to treat the early stages of idiopathic facial paralysis (Bell's palsy) in children, but their effectiveness is uncertain. We set out to determine if prednisolone improves the proportion of children with Bell's palsy with complete recovery at one month.

Methods

We conducted a double-blind, placebo-controlled, randomised trial of prednisolone in children presenting to emergency departments with Bell's palsy. Patients aged 6 months to less than 18 years, recruited within 72 hours after symptom onset, were randomly assigned to receive 10 days of treatment with oral prednisolone (approximately 1 mg/kg) or placebo. The primary outcome was complete recovery of facial function at 1 month rated on the House–Brackmann scale. Secondary outcomes included facial function, adverse events and pain up to 6 months. Target recruitment was n=540 (270 per group).

Results

Between 13 October 2015 to 23 August 2020, 187 children were randomised (94 to prednisolone and 93 to placebo) and included in the intention-to-treat analysis. At 1 month, the proportions of patients who had recovered facial function were 49% (n=43/87) in the prednisolone group compared with 57% (n=50/87) in the placebo group (risk difference -8.1%, 95% CI -22.8 to 6.7; adjusted odds ratio [aOR] 0.7, 95% CI 0.4 to 1.3). At 3 months these proportion were 90% (n=71/79) for the prednisolone group versus 85% (n=72/85) for the placebo group (risk difference 5.2%, 95%, CI -5.0 to 15.3; aOR 1.2, 95% CI 0.4 to 3.0) and at 6 months 99% (n=77/78) and 93% (n=76/82) respectively (risk difference 6.0%, 95% CI -0.1 to 12.2; aOR 3.0 95% CI 0.5 to 17.7) There were no serious adverse events and little evidence for group differences in secondary outcomes.

Discussion

In children with Bell's palsy the vast majority recover without treatment. The study, although underpowered, does not provide evidence that early treatment with prednisolone improves complete recovery.

Registration

Registered with the Australian New Zealand Clinical Trials Registry ACTRN12615000563561, registered 1 June 2015.

https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=368505&isReview=true

Classification of evidence

This study provides Class I evidence that for children with Bell's palsy, prednisolone does not significantly change recovery of complete facial function at one month. However, the study lacked the precision to exclude an important harm or benefit from prednisolone.

INTRODUCTION

Bell's palsy or acute idiopathic lower motor neurone facial paralysis is characterised by sudden onset paralysis or weakness of the muscles to one side of the face controlled by the facial nerve.[1] Population-based data from Northern California in children up to 18 years of age report an overall incidence rate of Bell's palsy of 18.8 per 100,000 person-years with incidence increasing with age, and higher in females.[2] In an emergency department (ED) based study of stroke mimics in children,[3] Bell's palsy was the third most frequent diagnosis in those with sudden onset neurological dysfunction.

In adults, up to 30% of untreated patients with Bell's palsy fail to make a complete recovery and may experience motor synkinesis.[4] In children, while 90% to 100% recover from Bell's palsy within 12 months, there is frequently a prolonged period of functional impairment, disfigurement and emotional distress.[4-8]

The main agents used for the treatment of Bell's palsy are corticosteroids such as prednisolone. The anti-inflammatory effect of corticosteroids is assumed to minimise facial nerve swelling, compression and damage within the temporal bone, therefore reducing the time to recovery and increasing the likelihood of ultimate complete recovery.[1,9] Two large, blinded randomised controlled trials (RCTs) of corticosteroids in adults[10,11] (combined n=1,309) and a meta-analysis[9] reported statistically and clinically significant improvements in the proportion of patients who reached complete recovery when treated with steroids compared with placebo.

Despite the conclusive evidence of benefit from corticosteroids in adults with Bell's palsy, there has only been one small RCT of corticosteroid use in children with Bell's palsy where 42 children received corticosteroids or no treatment.[6] Although all children fully recovered within 12 months regardless of treatment, corticosteroids appeared to hasten the time to recovery. The lack of a placebo, small patient numbers, and inclusion of only children with severe signs and symptoms at presentation limit the generalisability of these results. The lack of evidence on the utility of steroids in children with Bell's Palsy, has led to variable practice in their treatment.[7,12,13]

We set out to determine if prednisolone improves recovery of facial function in children with Bell's palsy by undertaking a multi-center placebo-controlled randomised trial. Our research question was whether prednisolone increased the proportion of children with Bell's palsy with complete recovery of facial function at one month using the House-Brackmann scale compared to placebo.[10,14]

METHODS

Study design

We undertook a phase III, double blinded, randomised, placebo-controlled superiority trial of prednisolone for the treatment of Bell's palsy in children. Participants were randomised in a 1:1 ratio to receive ~1 mg/kg/day of prednisolone up to a maximum dose of 50 mg (***eTable 1***), or matched placebo for 10 days. The study was conducted in 11 emergency departments (EDs) in the Paediatric Research in Emergency Departments International Collaborative (PREDICT) research network in Australia and New Zealand.[15] The central study site was the Murdoch Children's Research Institute in Melbourne (MCRI), Australia and the central study pharmacy was at the co-located Royal Children's Hospital (RCH), Melbourne, Australia. The study protocol has been previously published[16] (https://bmcpediatr.biomedcentral.com/articles/10.1186/s12887-016-0702-y) with key features presented below.

Standard protocol approvals, registrations and patient consents

The trial was approved by the institutional ethics committee at the RCH (HREC/15/RCHM/V4) and received governance approval by the institutional ethics offices at each participating site. Written informed consent was obtained for each participant from a parent or legal guardian and the child if deemed competent. The study was

registered with the Australian New Zealand Clinical Trials Registry ACTRN1261500056356, first registered 1 June 2015.

Participants

Patients presenting to participating EDs were considered for inclusion by ED clinical or research staff if aged between 6 months and less than 18 years with an ED clinician diagnosis of Bell's palsy and onset of facial weakness less than 72 hours before randomisation.

Exclusion criteria included possible contraindication to prednisolone, including active or latent tuberculosis, systemic fungal infection, known hypersensitivity to prednisolone or any of the excipients in the study medication, diminished cardiac function, diabetes mellitus, peptic ulcer or chronic renal failure, multiple sclerosis, recent active herpes zoster or chickenpox; use of any systemic or inhaled steroid within 2 weeks prior to the onset of symptoms; current or past oncological diagnosis; pregnancy or breast feeding; currently receiving concomitant medications in which prednisolone is contraindicated; immunisation with a live vaccine within the previous 1 month; requirement for a live vaccine within 6 weeks of the first dose of study drug; signs of upper motor neurone VII nerve weakness; acute otitis media concurrently or within 1 week prior to the onset of Bell's palsy symptoms; evidence of vesicles at the ear suggestive of Ramsay-Hunt syndrome; known facial trauma within 1 week prior to the onset of symptoms; any other condition at risk of being influenced by the study treatment or that might affect completion of the study; any concern about the ability to comply with the study protocol; and prior episode of Bell's palsy or prior randomisation into the study.

Randomisation and blinding

Participants were randomised in a 1:1 ratio to prednisolone or taste matched placebo packaged and labelled identically. An independent statistician generated the randomisation schedule using block randomisation with variable block sizes, stratified by site. This schedule was used by the central study pharmacist at the RCH to undertake the blinding, labelling and distribution of the study drugs to participating sites by putting together study packs of the required drug labelled with sequential study numbers for each site and dosing instructions. Randomisation was undertaken at the site by ED and research staff by selecting the lowest numbered study pack from the study drug store in the ED. Randomisation was blinded to trial participants, the investigator team, data management staff, and clinical staff.

Procedures

For the 10-day study treatment period following randomisation, participants received either ~1 mg/kg/day of prednisolone (based on patient weight categories) up to a maximum of 50 mg/day or a matched placebo. Prednisolone (Redipred®) and matched placebo was donated by Aspen Pharmacare Pty Ltd (St Leonards, NSW, Australia) who played no role in study design, execution, analysis or manuscript writing. The study drugs (prednisolone or placebo) were supplied based on a pre-calculated weight-based table as a once daily dose (***eTable 1***).

In the event of the presentation of a child with suspected Bell's palsy, ED staff at participating sites were asked to notify the senior medical doctor on duty who performed an initial assessment of potential eligibility. The pragmatic entry point into the study was the clinician decision to diagnose Bell's palsy, i.e. the point where the decision to use or not use steroids would occur in the clinical setting as well. If then thought to be eligible, the senior doctor or a member of the investigator team approached the participant and their parent/guardian(s) to inform them of the study, determine their interest in participating, confirmed eligibility and (where applicable) obtained written informed consent. The relevant clinical teams at each site received standardised, study specific education based on centrally developed education materials.

Following consent, demographics and relevant clinical and study information was collected. Following randomisation, ED clinicians administered the first dose of the study drug from the relevant study pack in the ED. The parent or guardian was then provided with the remaining study drug along with written instructions regarding dosing and storage.

Fourteen days after randomisation, the parent/guardian/participant received a phone call from the study team to assess medication compliance, adverse events and ongoing palsy symptoms. One month after randomisation, participants attended a visit at the study site where they had been recruited. If the participant was unable to attend the study site, this was completed via videoconferencing. A specialist clinician (a pediatric neurologist; otolaryngologist; pediatrician or emergency physician to accommodate site specific resources) reviewed the participant to exclude an alternative diagnosis for the Bell's palsy symptoms; determined House-Brackmann grade (the primary outcome) and the Sunnybrook scale of the Bell's palsy; determined the presence of synkinesis using the Synkinesis Assessment Questionnaire (SAQ), adverse events, ongoing palsy symptoms,

abnormal hearing, lacrimation and altered taste, the date of resolution of facial weakness (if resolved) as subjectively perceived by parent and any medical contact. A further follow-up assessment at 3 and 6 months was arranged for participants deemed at their previous visit not to be completely recovered (defined as a House-Brackmann score greater than 1). Participants deemed to have complete recovery at a prior visit (at 1 or 3 months) were instead asked to complete the subsequent follow-up assessment via telephone or online. Facial images were captured using video recording and still photographs at the time of randomisation and at all follow up visits.

Outcomes

The House-Brackmann scale provides gross assessment of facial function in a six-grade score where 1 is normal function and 6 is complete paralysis.[10,14] The Sunnybrook scale is a regionally weighted scale of facial function and assesses resting symmetry, voluntary movement, and synkinesis to produce a composite score of 0 to 100 where 0 is complete paralysis and 100 is normal function.[10,17,18] The primary outcome was complete recovery at 1 month post randomisation, defined as a House-Brackmann score of 1.[10,14] This outcome definition and timing of assessments was informed by limited available pediatric data,[5,6,13] indicating more rapid recovery in children than in adults.

Secondary outcomes included complete recovery of function using the House-Brackmann scale at 3 and 6 months and complete recovery on the Sunnybrook scale at 1, 3, and 6 months defined as a score of 100. We also assessed pain at 1, 3 and 6 months using a child assigned visual analogue scale or Faces Pain Scale Revised (for participants aged 5 and older) and using a parent assigned visual analogue scale (VAS).[19,20] Prevalence of synkinesis or autonomic dysfunction was assessed at 1, 3 and 6 months using the SAQ.[21] We assessed the emotional and functional wellbeing of the participant at 1, 3 and 6 months using the Pediatric Quality of Life Inventory (PedsQL)[22] and Child Health Utility 9D (CHU9D) scales.[23] Adverse events, compliance and adherence were captured at the 14 day and 1 month assessments.

Statistical analysis

Before the study, we expected 60% of children in the placebo arm to have complete recovery at 1 month. This was based on observational data[5,13] and a prior pediatric RCT.[6] A study in adults[10] deemed an improvement of 12% when treated with prednisolone compared with placebo to be a clinically important difference between

treatment groups. We therefore powered the study to find an increase in the proportion with complete recovery from 60% in the placebo group to 72%. With 80% power at 5% significance this required 244 subjects in each treatment group or 270 per group (540 in total) to allow for 10% loss to follow-up at 1 month. Due to lower than expected recruitment we extended the study by a year from the original plan and increased the number of participating sites. Enrolment was stopped when funding expired; we did not achieve the planned sample size.

Data were analysed on an intention-to-treat basis. Summaries of baseline and outcome variables are presented using the available data. Baseline characteristics are described by treatment group using median and interquartile range (IQR) for continuous outcomes and number and percentage for categorical outcomes. The primary outcome of complete recovery at 1 month post randomisation on the House-Brackmann scale is presented as the number and proportion in each treatment group, with a comparison between the groups presented as a difference in proportions and as odds ratio (OR) from a logistic regression model adjusted for site, with a 95% confidence interval (CI) for the hypothesis that there was no difference between the prednisolone and placebo group.

Participants who were deemed to have fully recovered according to the House-Brackmann scale (i.e., achieved a House-Brackmann score of 1) at the 1 month or subsequent visits were not required to attend the study site for the remaining study time points. These participants were assumed to be fully recovered at the later assessments and the House-Brackmann score at subsequent time points were set to 1.

Similarly, participants who were determined to be fully recovered on the Sunnybrook scale (score = 100) were assumed to have a score of 100 at later visits if their score was missing. Multiple imputation was used to handle missing data for the primary analysis of all outcomes using a single (joint) imputation model for 1 month outcomes, and separate imputation models for 3 and 6 month outcomes, conducted using fully conditional specification with 50 imputed datasets.[24] Binary variables were imputed using logistic regression, normally-distributed continuous variables using linear regression, non-normal continuous variables using predictive mean matching (k = 5), and multinomial logistic regression for nominal variables. Child sex, age, and weight, as well as time to treatment (<24h or ≥24h to 72h), ED site and baseline House-Brackmann score (severe = House-Brackmann grade 5 or 6, non-severe = House-Brackmann grade 1 to 4) were included in the imputation model to improve the accuracy of the imputed values. A complete case analysis was undertaken as a secondary analysis. As a sensitivity analysis, we repeated the analysis adjusted for age, sex, baseline severity of facial

nerve dysfunction (severe = House-Brackmann grade 5 or 6, non-severe = House-Brackmann grade 1 to 4) and time to treatment (<24h or ≥24h to 72h) as potentially important confounders.

For secondary outcomes binary analyses were presented as the number and proportion with the outcome in each treatment group, with comparisons between the groups presented as a difference in proportions and as ORs from logistic regression adjusted for site, with 95% CIs. Continuous outcomes are presented as median (IQR) within each treatment group. Again, we repeated the analysis adjusted for age, sex, baseline severity of facial nerve dysfunction and time to treatment as potentially important confounders, presenting adjusted odds ratios (aORs).

In pre-planned subgroup analyses, recovery according to the House-Brackmann scale was compared between the intervention groups in the subgroups defined by age (<12 years or ≥12 years), time to treatment (<24h or ≥24h to 72h) and initial severity (severe = House-Brackmann grade 5 or 6, non-severe = House-Brackmann grade 1 to 4) using the same methodology as described above. A full statistical analysis plan was published online prior to database closure.[25] The study had an independent data safety monitoring board, who were going to undertake a pre-planned interim analysis when 244 participants had primary outcome data available; this target was not reached.

De-identified data were managed using Research Electronic Data Capture (REDCap), hosted at MCRI and analysed using Stata 15.1 (Statacorp, College Station, Texas, USA).

Data availability

The authors support data sharing. Data from the BellPIC trial have used identifiable individual patient data that are subject to restriction due to ethics, consent, and privacy issues. Anonymised participant data and data dictionary will be available on request from the corresponding author where possible within these constraints for use.

RESULTS

From 7 October 2015 to 1 September 2020, 869 children were assessed for facial weakness with 332 ineligible, 164 excluded, 133 refusing consent and 52 missed (***Figure 1***). Reasons for ineligibility were symptoms present for 72 hrs or more (n=152), diagnosis other than Bell's palsy (n=138) and aged less than 6 months or more than 18 years (n=42). Reasons for exclusion were: previous episode of Bell's palsy or previously randomised (n=29),

contraindication to prednisolone (n=8), current use of inhaled or systemic steroids (n=42), current or past oncological diagnosis (n=5), currently receiving medications for which prednisolone was contraindicated (n=2), immunisation with a live vaccine within the previous 1 month (n=6), requirement for live vaccine within 6 weeks of first dose of prednisolone (n=2), signs of upper motor neuron VII nerve weakness (n=4), current or recent otitis media (n=32), evidence of vesicles on the ear drum or canal (n=6), significant facial trauma within 1 week prior to symptoms appearing (n=3), and assessed as unable to attend follow up or complete the study (n=25).

Figure 1 shows a flowchart of trial participation. Of 188 participants enrolled and consented, 187 were randomised with one family withdrawing consent after enrolment and prior to randomisation. There were no further withdrawals of consent. One patient was enrolled and had received study drug but was later found to have had Bell's palsy previously and therefore was technically ineligible. This participant was followed up as per the protocol and was included in the analysis. One randomised participant received no drug after randomisation (refused study drug; included in analysis) and none received the incorrect study drug. Of the 187 children randomised 93 were assigned to prednisolone and 94 to placebo and all were included in the intention-to-treat analysis. Thirteen (7%) had no primary outcome recorded at 1 month, including the one participant who did not receive any study drug; therefore 174 (93%) were included in the complete case analysis.

Table 1 shows the baseline characteristics of the study participants by treatment arm which were similar in terms of sex, time from onset of symptoms to treatment and House-Brackmann scores. Median age at baseline in the intention-to-treat population was 9.9 years (IQR 5.1 to 12.9), 51.9% were female, median time to treatment was 24.0 hours (IQR=11.5 to 48.0) and median House-Brackmann score at enrolment was 4 (IQR=3 to 4). Median age in children who received prednisolone was 11.1 years (IQR 5.2 to 14.0) and for those receiving placebo was 9.4 years (IQR 5.1 to 11.8).

In terms of medication compliance, 14 (7.5%) participants received less than all 10 required doses of study drug but at least one dose, five (2.7%) participants received more than 10 doses of study drug (with 4 receiving 1 or 2 extra doses). One participant received 20 doses of their study drug. Due to safety concerns, the randomisation code was broken, revealing that they had received prednisolone, and the participant was placed on a steroid taper with uneventful recovery. One participant was diagnosed with leukaemia after completion of the study

drugs; the randomisation code was broken and the patient was found to have received prednisolone. The participant was lost to follow up in terms of primary and secondary outcomes but included in the intention-to-treat analysis. One participant developed bilateral Bell's palsy after completing the study drug (third of three where randomisation code was broken); MRI imaging confirmed Bell's palsy. The participant continued in the study. One participant developed Ramsey-Hunt syndrome post randomisation. The participant received an antiviral agent after completing the study drug and continued in the study.

At 1 month, the proportions of patients who had recovered facial function (House-Brackmann grade 1) (***Table 2, Figure 2***) were 49% (n=43/87) in the prednisolone group compared with 58% (n=50/87) in the placebo group (risk difference -7.4%, 95% CI -22.5 to 7.6; aOR 0.7, 95% CI 0.4 to 1.4). Data on recovery rates by age (<12 years or ≥12 years), time to treatment (≤24h or >24h to 72h) and initial severity (House-Brackmann grade 5 or 6 vs. 1 to 4) are shown in ***eTable 2***. Recovery in children <12 years at 1 month was 43% for prednisolone versus 60% for placebo (risk difference -16.0%, 95% CI -34.2 to 2.2; aOR 0.5, 95% CI 0.3 to 1.1) and in children ≥12 years 58% versus 50% respectively (risk difference 8.9%, 95% CI -18.2 to 35.9; aOR 1.4, 95% CI 0.5 to 4.3).

At 3 months the proportion of participants with complete recovery (House-Brackmann grade 1) was 90% (n=71/79) for the prednisolone group versus 85% (n=72/85) for the placebo group (risk difference 3.4%, 95%, CI -7.6 to 14.4; aOR 1.3, 95% CI 0.5 to 3.4) and at 6 months 99% (n=77/78) versus 93% (n=76/82) respectively (risk difference 5.1%, 95% CI -2.6 to 12.8; aOR 3.1 95% CI 0.5 to 20.2) (***Table 3***). Recovery in children ≥12 years was 94% versus 75% and 97% versus 84% in prednisolone versus placebo at 3 months and 6 months respectively (***eTable 2)***. Complete case analysis and a secondary sensitivity analysis adjusted for age, sex, baseline severity of facial nerve dysfunction and time to treatment showed similar results.

A similar pattern of results was seen with complete recovery of facial function on the Sunnybrook scale (***Table 2***). Synkinesis and pain were very low at all time points over the 6 month follow up period (***Table 3***).

Adverse events not attributed to the underlying disease or unrelated to disease or intervention are shown in ***Table 4***. There were no serious adverse events. The most frequent adverse events noted in the prednisolone group were transient change in behaviour and increased appetite.

This study provides Class I evidence that for children with Bell's palsy, prednisolone does not significantly change recovery of complete facial function at one month. However, the study lacked the precision to exclude an important harm or benefit from prednisolone.

DISCUSSION

We found that children with Bell's palsy generally have a good functional outcome with 57% of placebo participants having complete recovery at 1 month and 93% at 6 months. The study was underpowered with only 187 participants recruited versus the planned 540. Despite this we found little evidence that treatment with prednisolone within 72 hours of the onset of symptoms increased the rate of complete recovery of facial function at 1, 3 and 6 months by a clinically relevant amount.

Two major trials[10,11] and a subsequent systematic review[9] have indicated that corticosteroid use in adults is associated with improved outcome for Bell's palsy compared with placebo. Similar definitive evidence is not available for children and to date their care has often been extrapolated from adult data. Based on prior reviews there are no prior placebo-controlled trials of corticosteroid use in children.[6,26] There are numerous retrospective and prospective cohort studies, but the only randomised trial in children by Unüvar et al[6] was single center and not placebo controlled. In that trial, while all children fully recovered within 12 months regardless of treatment, consistent with our trial, more children in the methylprednisolone group had recovered at 4 and 6 months compared with the no treatment group (86% vs 72% at 4 months and 100% vs 85% at 6 months).

We used the House-Brackmann scale to assess recovery of facial function similar to the two largest adult RCTs,[10,11] and the prior RCT in children.[6] The House-Brackmann scale is easily applied and widely used but there is some debate on the optimal scale to use in Bell's palsy and data on use in children are limited.[6,10,11,27] The House-Brackmann scale provides a single global assessment, whereas the Sunnybrook scale provides a regionally weighted facial assessment including resting symmetry, degree of voluntary movement and synkinesis. Our study indicates that both Sunnybrook and House-Brackmann assessed complete facial recovery similarly (House-Brackmann 1 or Sunnybrook 100). In adults, complete recovery over all time points using the Sunnybrook is somewhat lower than with House-Brackmann.[11]

In adult RCTs of prednisolone versus placebo for the management of Bell's palsy a group difference of between 10-12% has been considered clinically meaningful.[10] We powered our study to find an improvement of 12% with prednisolone treatment. Although not meeting our calculated sample size, mainly due to exclusion criteria of presentation after 72 hours and pre-treatment with prednisolone, the point estimate for the proportion with complete recovery was higher in the placebo group. In addition, the 95% CI around the difference between the groups for our primary outcome of complete recovery of facial paralysis measured via House-Brackmann at 1 month did not include a 10-12% improvement with prednisolone treatment (difference between groups -7.4%, 95% CI -22.5 to 7.6%). However, in this underpowered sample the 95% CI of all secondary outcomes measuring recovery of facial function (House-Brackmann at 3 and 6 months; Sunnybrook at 1, 3 and 6 months) all included the possibility of a 10-12% improvement. The results of these secondary outcomes suggest caution in interpreting the primary outcome result in isolation as evidence that prednisolone provides no clinical benefit in the management of Bell's palsy in children.

There is currently little evidence for the optimal prednisolone dose in children with Bell's palsy with doses reported from 0.5 mg/kg up to 2 mg/kg.[13,26] We chose 1 mg/kg for 10 days which is consistent with two large adult RCTs which used 50 mg prednisolone daily for 10 days,[10] or 60 mg prednisolone daily for 5 days then weaning over 5 days[11] and the only other pediatric RCT used methylprednisolone 1 mg/kg/day (equivalent to 1.25 mg/kg/day prednisolone) for 10 days, then weaned over 3-5 days.[6] In our study adverse events from this dose were limited to temporary behaviour changes and increased appetite.[28]

Baseline facial pain in children with Bell's palsy was infrequent and mild if present, with few children having pain at follow up at any time point. Furthermore, fewer children developed synkinesis over the 6 month study period in either group than in adults.[9] Together these findings indicate that Bell's palsy in children is a milder disease than that seen in adults, with morbidity primarily confined to facial weakness and that recovery is considerably more rapid and more likely to be complete, thus reducing the need for treatment.

The decision to use prednisolone to treat Bell's palsy in children must also be considered in light of potential side effects. While as expected, on the whole these were mild in participants, in Bell's palsy there is the increased concern that corticosteroid use may mask facial paralysis as first presentation of an oncological diagnosis, both delaying diagnosis and potentially complicating management and prognosis.[29] This event

occurred in one patient enrolled in the RCT, and a further four patients screened as part of the RCT. The potential effect of prednisolone on the oncological presentations should ensure that clinicians only use prednisolone in Bell's palsy in children when there is clear evidence of clinically meaningful efficacy.

The main limitation of the study was that it study was underpowered compared to the original sample size calculations which reduced our power to identify group differences in all outcomes and analyses. The main reasons patients were ineligible for inclusion were late presentation to the ED (more than 72 hours after onset) and treatment with prednisolone by a general practitioner before presenting to the ED. Further limitations include that the study was conducted in EDs at mainly tertiary centers. If more severely affected patients were referred selection bias may have resulted in our trial recruiting more patients less likely to respond to steroids. In addition, while research and site clinical staff received standardised education for the study, we did not test for interrater reliability of clinician diagnosis of Bell's palsy or their use of the rating scales. Lyme disease, which does not exist in Australasia, can cause facial paralysis and may be an important consideration in early diagnostic and management decisions in patients considered for a treatment in Lyme endemic areas.[26,30]

Despite our insufficient sample size the 95% CIs around the effect size for the primary outcome of complete recovery from Bell's palsy at 1 month ranged from 22% in favour of placebo to only 6% in favour of prednisolone. There was also high spontaneous recovery by 6 months, low rates of morbidity from pain or synkinesis, clinical concern regarding prescribing of prednisolone in children with Bell's palsy that may represent the first presentation of an oncological diagnosis and concern regarding the use of prednisolone in Lyme disease. Together these lead us to conclude that there is no more than a marginal likelihood that prednisolone is beneficial when used in Bell's palsy in children.

WNL-2022-201093_etab --- http://links.lww.com/WNL/C272

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Table 1: Baseline characteristics of the patients in the intention-to-treat analysis

	Prednisolone			Placebo		
Child age [years]						
N Mdn IQR	93	11.13	(5.17-14.01)	94	9.44	(5.09-11.84)
Child age [years], N n %						
6 mo to <12 y	93	54	58.06	94	73	77.66
12 y to <18 y	93	39	41.94	94	21	22.34
Child sex, N n %						
Male	93	45	48.39	94	45	47.87
Female	93	48	51.61	94	49	52.13
Ethnicity, N n %						
Non-indigenous	93	89	95.70	94	86	91.49
Indigenous	93	4	4.30	94	8	8.51
Child weight [kgs]						
N Mdn IQR	93	46.20	(21.50-61.00)	93	34.40	(19.90-49.00)
Length of illness [hours]						
N Mdn IQR	89	24.00	(12.00-48.00)	91	24.00	(10.00-36.00)
Length of illness [hours], N n %						
0 to 24 h	92	37	40.22	93	45	48.39
>24 h to 48 h	92	38	41.30	93	36	38.71
>48 h to 72 h	92	17	18.48	93	12	12.90
Side of the facial weakness, N n %						
Left	93	47	50.54	94	55	58.51
Right	93	46	49.46	94	39	41.49
Symptoms on presentation						
House-Brackmann, N n %						
Non-severe (II to IV)	93	85	91.40	94	81	86.17
Severe (V and VI)	93	8	8.60	94	13	13.83
House-Brackmann score						
N Mdn IQR	93	3.00	(3.00-4.00)	94	4.00	(3.00-4.00)
VAS score - Child						
N Mdn IQR	72	0.00	(0.00-1.50)	70	0.00	(0.00-1.00)
Revised Faces Pain Scale - Child						
N Mdn IQR	13	0.00	(0.00-0.00)	20	0.00	(0.00-2.00)
VAS score - Parent						
N Mdn IQR	78	0.00	(0.00-1.00)	83	0.00	(0.00-1.00)

N number Mdn median IQR interquartile range
VAS visual analogue scale

Table 2: Patients in the intention-to-treat analysis with complete recovery per follow up

	Prednisolone				Placebo				Unadjusted %		Adjusted	
	n	N	%	(95%CI)	n	N	%	(95%CI)	difference	(95%CI)	OR	(95%CI)
Primary Outcome												
1 Month												
House-Brackmann scale	43	87	49.43	(38.53, 60.36)	50	87	57.47	(46.41, 68.01)	-7.44	(-22.46, 7.58)	0.74	(0.40, 1.36)
Secondary Outcomes												
1 Month												
Sunnybrook scale	42	82	51.22	(39.92, 62.42)	45	84	53.57	(42.35, 64.53)	-2.19	(-17.68, 13.29)	0.92	(0.49, 1.70)
3 Months												
House-Brackmann scale	71	79	89.87	(81.02, 95.53)	72	85	84.71	(75.27, 91.60)	3.40	(-7.57, 14.37)	1.33	(0.53, 3.37)
Sunnybrook scale	66	75	88.00	(78.44, 94.36)	66	79	83.54	(73.51, 90.94)	2.26	(-9.57, 14.10)	1.19	(0.49, 2.84)
6 Months												
House-Brackmann scale	77	78	98.72	(93.06, 99.97)	76	82	92.68	(84.75, 97.27)	5.12	(-2.57, 12.80)	3.06	(0.46, 20.22)
Sunnybrook scale	70	73	95.89	(88.46, 99.14)	70	76	92.11	(83.60, 97.05)	3.10	(-6.85, 13.05)	1.58	(0.38, 6.56)

CI confidence interval

Table 4: Adverse Events

	Prednisolone	Placebo	Total
Change in behaviour	6	3	9
Increased appetite	8	1	9
Headache	3	4	7
Fatigue	2	3	5
Rash	1	4	5
Insomnia	2	2	4
Decrease appetite	0	2	2
Diarrhoea	2	0	2
Abdominal Pain	1	0	1
Change in vision	1	0	1
Epigastric	1	0	1
Hair loss	0	1	1
Headache and change in vision*	1	0	1
Muscle aches	1	0	1
Nausea	0	1	1
Polyuria	1	0	1
Vomiting	1	0	1
TOTAL	**31**	**21**	**52**

Legend:

Figure 1: Trial profile

Trial profile with participant flow from assessment of eligibility to inclusion in intention-to-treat analysis.

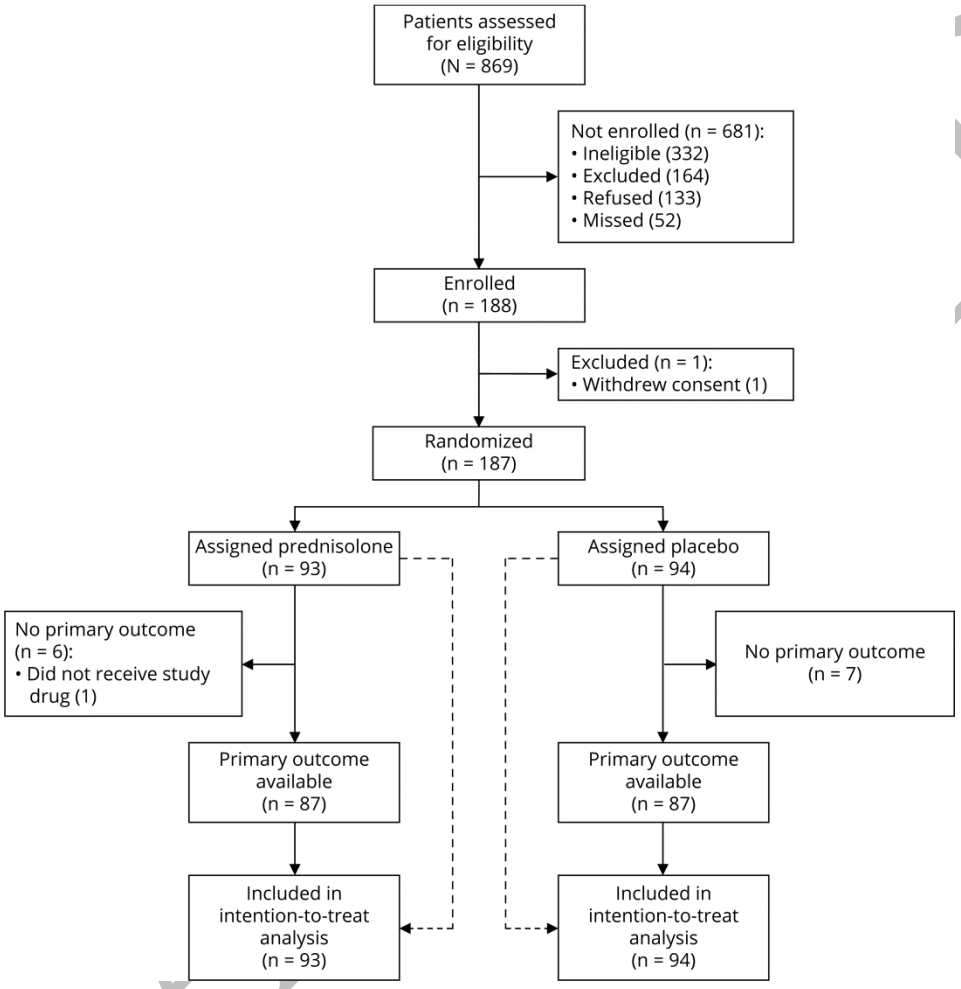

Figure 2: Recovery measured by House-Brackmann scale at 1, 3 and 6 months

Graph shows percentage of participants with recovery of facial function in prednisolone and placebo groups from randomisation (time 0) to 1,3 and 6 months as measured by achieving a House-Brackmann scale score of 1.