Journal of Pediatric Surgery 50 (2015) 1590–1594

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Review Articles

Postoperative steroid therapy for biliary atresia: Systematic review and meta-analysis☆,☆☆,★,★★,☆☆☆

Yong Chen [a], Shireen Anne Nah [a], Liwei Chiang [a], Gita Krishnaswamy [b], Yee Low [a,*]

[a] Department of Pediatric Surgery. KK Women's & Children's Hospital, Singapore
[b] Centre for Quantitative Medicine, Duke-NUS Graduate Medical School, Singapore

ARTICLE INFO

Article history:
Received 2 April 2015
Accepted 18 May 2015

Key words:
Biliary atresia
Steroid
Kasai procedure
Pediatric
Jaundice clearance

ABSTRACT

Background/Objectives: Adjuvant steroid therapy has become popular in the postoperative management of biliary atresia. However, the benefits of steroid therapy are still not clear. We performed a systematic review and meta-analysis to determine the effect of steroids on bile drainage posthepatoportoenterostomy.
Methods: Studies published from 1968 to 2014 were searched from MEDLINE, EMBASE, Google scholar and Cochrane databases. A meta-analysis of randomized controlled trials (RCT) and observational studies comparing bile drainage between steroid and nonsteroid therapies posthepatoportoenterostomy was performed.
Results: Seven studies (2 RCTs and 5 observational studies) were included, comprising 259 cases of nonsteroid and 228 cases of steroid therapies. There was no statistical improvement in jaundice clearance in the steroid group [pooled odds ratio (OR) = 1.51; 95% confidence interval (CI) 0.95–2.41; $P = 0.08$; $I^2 = 30\%$]. Among 7 studies, 4 studies applied similar moderate high-dose steroid regimens (prednisolone 4–5 mg/kg/day for 1–2 weeks followed by weeks of tapering dosage). However, these moderate high-dose regimens demonstrated improved jaundice clearance at 6 months posthepatoportoenterostomy (pooled OR = 1.59; 95% CI 1.03–2.45; $P = 0.04$; $I^2 = 0\%$). A subgroup analysis also showed that the effect of those moderate high-dose steroids was more pronounced in infants operated on by 70 days of age (pooled OR = 1.86; 95% CI 1.08–3.22; $P = 0.03$; $I^2 = 0\%$).
Conclusion: Moderate high-dose steroid therapy improves jaundice clearance, especially for infants who undergo hepatoportoenterostomy by 70 days of age. However, more RCTs with longer follow-up are necessary to demonstrate the effect of steroids on the long-term outcomes of biliary atresia.

Adjuvant steroid therapy has become popular in the postoperative management of biliary atresia (BA). Its anti-inflammatory properties are thought to reduce periductal inflammation and oedema, thus improving biliary drainage. However, detractors of steroid therapy argue that its beneficial effects are unproven, and its routine administration subjects patients to the small yet not negligible side effects of steroids. Studies describing various steroid regimens have been published, including two meta-analyses and a recent randomized controlled trial (RCT) without demonstrating clear benefits of steroid therapy in BA [1–3]. We performed a systematic review and meta-analysis to determine the effect of steroids on bile drainage posthepatoportoenterostomy, and included the recent RCT, which was not included in the 2 previous published meta-analyses.

1. Methods

1.1. Study selection

Articles from January 1968 to August 2014 in the MEDLINE, EMBASE, Google scholar and Cochrane databases were searched systematically using different combinations of the following terms: "biliary atresia", "hepatoportoenterostomy", "KASAI procedure", "steroid", "corticosteroid", "dexamethasone", "prednisolone" and "hydrocortisone". The "related articles" function was used to widen the search. The reference lists of the full articles were also manually searched to identify additional eligible studies. Owning to the paucity of available randomized control trials addressing the study question, observational clinical studies (OCS) were also included. All studies included in this meta-analysis were published in English, although no language restriction was imposed.

Abbreviations: BA, biliary atresia; CI, confidence interval; OCS, observational clinical studies; OR, odds ratio; RCT, randomized controlled trials.

☆ Funding source: No funding was secured for this study.
☆☆ Financial disclosure: The authors have no financial relationships relevant to this article to disclose.
★ Conflict of interest: The authors have no conflict of interest to disclose.
★★ IRB approval: This study was deemed exempt by the institutional review board.
☆☆☆ Author's contribution: Dr Chen, Dr Nah, Dr Chiang and Dr Low contributed to the design, planning, and writing of the article. Dr Chen, Dr Nah and Dr Krishnaswamy extracted the data and performed the analysis. Dr Chen and Dr Nah drafted the initial manuscript which was jointly approved by all the authors. Dr Low is the guarantor of the work.

* Corresponding author at: Department of Paediatric Surgery, KK Women's & Children's Hospital, 100 Bukit Timah Road, Singapore 229899. Tel.: +65 6394 1134; fax: +65 6291 0161.
E-mail address: low.yee@kkh.com.sg (Y. Low).

http://dx.doi.org/10.1016/j.jpedsurg.2015.05.016
0022-3468/

1.2. Data extraction

Two reviewers (C.Y. and S.N.) independently assessed selected studies, extracted and tabulated data from each article: first author, year of publication, study design, sample size, follow-up period, mean age at operation, total bilirubin before operation, steroid regimen, and outcome measure (jaundice clearance at 6 months after operation). The reviewers reached consensus at each stage of the screening process.

1.3. Inclusion criteria

To enter the analysis, studies had to (1) report the results of steroid therapy for infants who underwent hepatoportoenterostomy; (2) contain comparative data for the steroid treatment group and the nonsteroid treatment group (treated with placebo or non-treatment); (3) report on the outcome measures mentioned above; and (4) be published as a full paper in a journal, not as a meeting abstract or review.

1.4. Exclusion criteria

The following criteria were used to exclude studies:

(1) Studies with inconsistent steroid treatment regimens, e.g., inclusion of different steroid dosages in the studied group or usage of predetermined steroid doses without calculation based on patient weight [4–6]
(2) Studies which compared combined adjuvant therapies, such as steroid and ursodeoxycholic acid, with the non-treatment group [7]
(3) Studies which had no sufficient outcome data to calculate odds ratios [8]
(4) Overlapping studies from the same institution [9,10]. In these cases, direct communication with the author of both studies provided access to the details of the overlapping data which were then removed to avoid duplication of data. [10].

1.4.1. Definition of steroid dosage

There is no consensus on what constitutes 'standard' dosage nor 'low' or 'high' dosage regimens. For the purpose of our analysis, we used categories of steroid dosage as defined by Davenport et al. [10].

1.5. Assessment of methodological quality of included studies

All OCSs were cohort studies for which the Newcastle–Ottawa scale (total 9 stars) was used to assess the methodological quality. Studies with low risk of bias were allocated ≥7 stars, moderate risk with 4–6 stars and high risk with ≤3 stars. The RCT was evaluated using the Jadad score (total 5 points); scores above 3 were considered high quality.

1.6. Statistical analysis

Pooled odds ratios (OR) were calculated for jaundice clearance using the Mantel–Haenszel method. The confidence interval (CI) was established at 95% and *P*-values of less than or equal to 0.05 were considered statistically significant.

Statistical heterogeneity was assessed using I^2. A fixed effects model was used if $I^2 < 25\%$ and a random effects model was used if $I^2 \geq 25\%$.

Sensitivity analysis was performed by omitting 2 studies with very high doses of steroid treatment and one study with low steroid dosage, keeping the studies with moderate-high steroid regimen (prednisolone 4–5 mg/kg/day for 1–2 weeks followed by weeks of tapering dosage) to determine the effect of this specific steroid regimen on the outcome of BA.

Statistical analysis was performed using Review Manager 5.2 (Cochrane Collaboration).

2. Results

2.1. Study characteristics

Twelve studies met the inclusion criteria. Five studies were removed based on our exclusion criteria, leaving 2 RCT and 5 OCS for meta-analysis [3,9–14] (Fig. 1; Table 1).

Our study included 487 patients: 259 cases received standard nonsteroid treatment and 228 cases received steroid therapies after KASAI procedure. The steroid therapy regimens varied among studies (Table 1). One RCT study (Davenport 2007) [9] used low doses of steroids (prednisolone 2 mg/kg/day) in the treatment group. Another study from same center (Davenport 2013) compared both high dose (prednisolone 5 mg/kg/day) and low dose steroid (prednisolone 2 mg/kg/day) treatment with the nonsteroid group [10]. As part of the data (the low-dose steroid and placebo groups) of the 2013 study overlapped with his previous RCT study, the duplicated data were removed from meta-analysis. The remaining 5 studies applied high doses of steroids in the treatment group. A treatment regimen of prednisolone 4–5 mg/kg/day for 1–2 weeks followed by weeks of tapering dosage was the most commonly used high dose steroid regimen and was adopted by 4 studies [3,10–12]. Two studies used very high dose steroid pulsed therapy with initial doses of methylprednisonone 10 mg/kg/day, which were quickly tapered down to low dose oral steroids over 5–7 days [13,14]. The mean age at surgery was below 90 days of life, except for one study [11]. There was no statistical difference when comparing mean age at hepatoenterostomy between steroid and nonsteroid groups among the selected studies. The total serum bilirubin levels before hepatoportoenterostomy were also similar between the steroid and nonsteroid groups in selected studies. The definition of jaundice clearance varied slightly between studies, ranging from 17.1 to 34.2 μmol/L. All studies reported the jaundice clearance at six months posthepatoportoenterostomy except for Meyers et al.'s [14] study which reported jaundice clearance at 3–4 months postoperation.

2.2. Methodological quality of included studies

In general, the quality of the included studies was satisfactory. Two cohort studies were given 5–6 stars on Newcastle–Ottawa Scale, corresponding to a moderate risk of bias. Three cohort studies exhibited a low risk of bias with scores of 7–8 stars. The 2 RCTs in this meta-analysis were also considered high quality with Jadad scores of 4 and 5 respectively (Appendix).

2.3. Effect of steroid therapy on jaundice clearance posthepatoportoenterostomy

All 7 studies reported jaundice clearance at 3–6 months posthepatoportoenterostomy. A total of 57.0% (130/228) of steroid-treated patients achieved jaundice clearance compared to 46.3% (130/259) in the control group. There was no significant difference between the two groups [pooled OR = 1.51; 95% CI 0.95–2.41; $P = 0.08$). A random effects model was used in the meta-analysis owning to the high heterogeneity ($I^2 = 30\%$) (Fig. 2).

2.4. Effect of moderate-high steroids on jaundice clearance posthepatoportoenterostomy

Among 6 studies with high-dose steroid treatment, two studies using very high initial steroid regimens (methylpredisolone 10 mg/kg/day) exhibited significant high heterogeneity of jaundice clearance when compared to the rest (Fig. 2) [13,14]. Therefore, a sensitivity study was performed by removing these 2 studies and a subgroup of patients receiving low dose steroid therapy in another study [10], leaving 4 studies with similar moderate-high dose steroid treatment (prednisolone 4–5 mg/kg/day). The moderate-high dose steroid