DOI:10.1111/hpb.12066 HPB

REVIEW ARTICLE

Use of pre-operative steroids in liver resection: a systematic review and meta-analysis

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Abstract

Background: By attenuating the systemic inflammatory response to major surgery, the pre-operative administration of steroids may reduce the incidence of complications.

Methods: A systematic review was conducted to identify randomized controlled trials (RCT) comparing pre-operative steroid administration with placebo during a liver resection. Meta-analyses were performed.

Results: Five RCTs were identified including a total of 379 patients. Pre-operative steroids were associated with statistically significant reductions in the levels of serum bilirubin and interleukin 6 (IL-6) on post-operative day one. There was a trend towards a lower incidence of post-operative complications and prothrombin time (PT), but this did not reach statistical significance.

Conclusion: Pre-operative steroids may be associated with a clinically significant benefit in liver resection.

Received 15 October 2012; accepted 5 December 2012

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Introduction

Major surgery is associated with an acute systemic inflammatory response mediated by endogenously generated cytokines and free radicals.[1,2] When excessive or uncontrolled this may lead to the systemic inflammatory response syndrome (SIRS).[3] The degree of SIRS after surgery may correlate with post-operative morbidity, mortality and a delayed return to function.[4] There has been interest in how this response may be modified in other major surgical procedures.[5,6] A liver resection is a procedure which may be associated with a marked cytokine response, that may be potentiated by the ischaemia–reperfusion injury caused by portal triad clamping and other methods of vascular control used in liver surgery.[7–9] Steroids are known to have significant analgesic[10] and antiemetic[11–13] properties, but their immunological and anti-inflammatory effects may improve the outcomes of a liver resection. It has been postulated that the peri-operative use of steroids may decrease the cytokine response and thus improve surgical outcomes.[14] The potential for the benefit of the use of steroids in liver surgery is supported by experimental studies.[15–17] Nevertheless, the utility of pre-operative steroid use in clinical liver resection remains controversial and their use is not a widespread practice. The aim of this systematic review and meta-analysis was to critically appraise the available evidence, with particular reference to randomized controlled trials (RCT).

Methods

A systematic literature search was independently conducted by two authors (A.J.R. and V.L.). The following electronic databases were searched: Medline (1950–2012), Embase (1974–2012), Cochrane Controlled trials Register and the science citation index. Combinations of medical subject headings (MeSH) as well as key words were used including the following: glucocorticoids, prednisone, methylprednisone, dexamethasone, steroids, predniso$, methylprednis$, liver surgery, hepatic resection, liver resection, hemihepatectomy and hepatectomy.

The literature search was not restricted by language or year of publication but was restricted to human trials. The last search was done on the 26 March 2012. A manual search was done of all the relevant articles and independent experts were contacted to retrieve other relevant articles.

Study selection and primary endpoints

Only RCTs comparing peri-operative steroid administration with placebo were included in the review. Studies describing paediatric

Table 1 Summary of randomized controlled trials analysed

First author	Institution	Year	Steroids administration regime	Steroids group number of patients	Placebo group number of patients	Total number of patients
Yamashita	Fukuoka, Japan	2001	MP 500 mg 2 h prior to surgery	17	16	33
Muratore	Torino, Italy	2003	MP 30 mg/kg 30 min prior to surgery	25	28	53
Aldrighetti	Milan, Italy	2006	MP 500 mg prior to induction of anaesthesia	36	37	73
Schmidt	Berlin, Germany	2007	MP 30 mg/kg 90 min prior to surgery	10	10	20
Hayashi	Tokyo, Japan	2011	MP 500 mg prior to hepatic pedicle clamping 300 mg on post-operative day 1 200 mg on post-operative day 2 100 mg on post-operative day 3	102	98	200
				190	189	379

MP, Methylprednisolone.

liver resections, cadaveric liver transplantation or laparoscopic liver resection were excluded, as were animal studies. The primary end points analysed were in-hospital mortality and complications. The secondary end points analysed were prothrombin time (PT), level of serum bilirubin and level of serum interleukin 6 (IL-6) on the first post-operative day. Those studies with insufficient data relating to the defined primary and secondary outcomes were excluded. The total number of complications was recorded as reported in the original papers and comprised myocardial infarction, chest infection, bile leak, intra-abdominal collections or pulmonary embolus. The recording was in accordance with the PRISMA criteria.[18] Two reviewers independently performed article selection and these were reviewed by the third author (J.L.). The methodological quality of studies was assessed using the Cochrane Collaboration's tool for assessing the risk of bias[19] using the following criteria: adequate sequence generation, allocation concealment, blinding, addressing of incomplete data and whether the article appeared to be free of selective reporting and other biases.

Statistical analysis

Meta-analyses were performed using Revman 5.1 (Review manager version 5.1; Cochrane collaboration 2011). Primary outcomes were expressed as an odds ratio (OR) with 95% confidence intervals (CIs) derived by the mean difference. A random effects model was used for the analysis. The Mantel–Haenzsel method was used for dichotomous outcomes and the inverse variance method was used for continuous outcomes. Heterogeneity was assessed using Cochran's Q statistic and an I^2 statistic, where values of 25% or less were considered to indicate low heterogeneity and values of 75% or more were taken to indicate high heterogeneity.[20] Forrest plots were constructed with *P*-values of less than 0.2 considered to be statistically significant.

Results

Description of studies

Five studies met the predefined inclusion criteria, were included in the meta-analysis and are summarized in Table 1.[21–25] The search strategy results are shown in Fig. 1. One group published three papers covering the same group of patients. Two of these studies were rejected[26,27] and only one study was included.[23] Another study that focused mainly on renal function after cadaveric liver transplantation was excluded.[28] Of the five included studies, two came from Japan, two from Italy and one from Germany. There were a total of 379 patients, with 190 patients in the pre-operative steroid group and 189 in the placebo group. More than half of the patients came from one study. There was no mortality reported in any of the analysed papers. Only one study used a classification of complication severity,[25] albeit not standardized. Standardized definitions of complications in liver surgery[29–31] or of complication severity[32] were not used in any study. The characteristics of the procedures (extent of resection, method of transaction, use, type and duration of vascular control) and patients are summarized in Table 2. The indications for liver resection are set out in Table 3.

Study quality

There was statistically significant heterogeneity observed in the analysis of length of stay (I^2 = 77%), level of bilirubin on post-operative day 1 (I^2 = 85%), PT on post-operative day 1 (I^2 = 76%) and IL-6 on post-operative day 1 (I^2 = 93%) but not with respect to complications (I^2 = 0%). Given the small number of studies, funnel plot analysis could not be reliably interpreted and was not performed. A risk of bias diagram is shown in Fig. 2. Only one study reported on all the parameters analysed.[23] No study was deficient in reporting on more than two parameters.

Primary study endpoints

Data were available for all studies. There was no mortality in either group. There was a trend towards a reduction in the incidence of post-operative complications with steroid administration (Fig. 3a), but this did not reach statistical significance (*P* = 0.09, OR = 0.68 95% CI 0.44 to 1.06).

Secondary study endpoints

Data were available from all five studies with regard to length of stay (Fig. 3b), post-operative serum bilirubin (Fig. 3c) and serum