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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.

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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

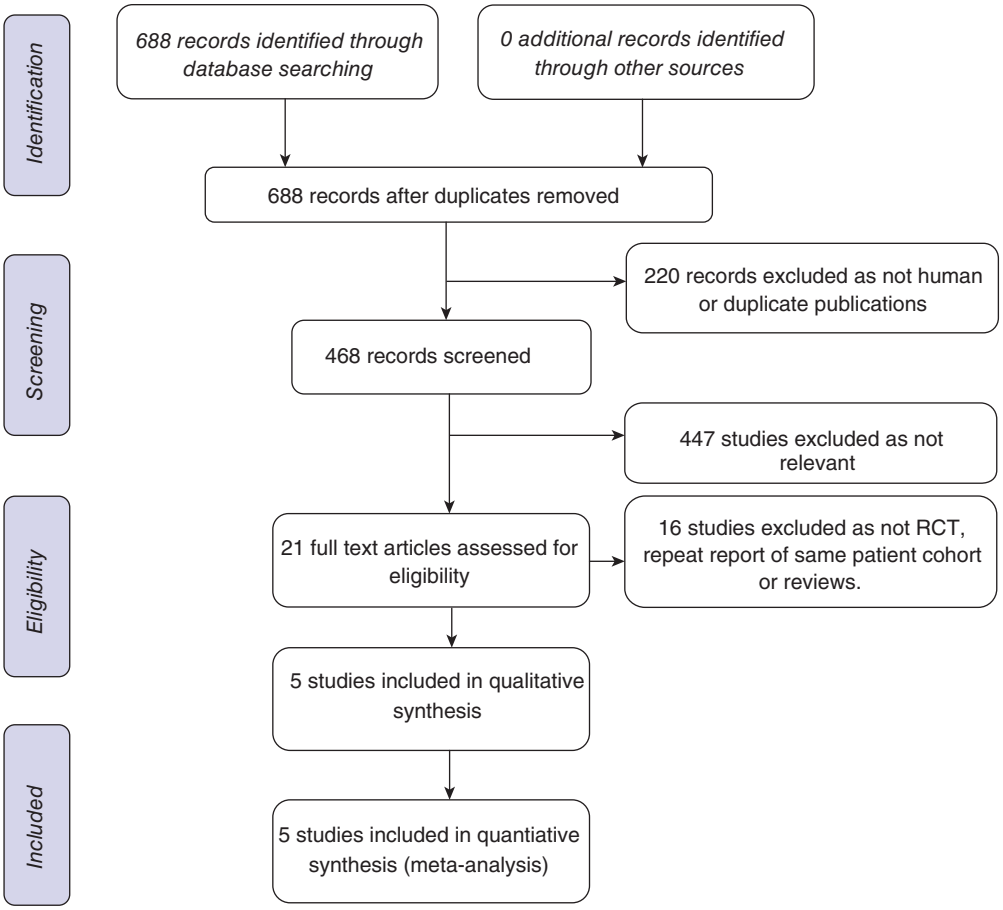

Figure 1 Flow chart showing the search strategy used to identify studies. RCT, randomized controlled trial

Table 2 Summary of characteristics of procedures and patients included in the studies

First author	Group	Major resection[a]	Resection technique[b]	Vascular control[b]	Ischaemic time (mins)	Cirrhosis
Yamashita	Steroids	5/17	NS	PTC or HVE with TVE	NS	NS
	Placebo	6/16			NS	NS
Muratore	Steroids	13/25	KC or UD	PTC (continuous)	41.4 (15.9)[c]	7/25
	Placebo	15/28			37.3 (17.8)[c]	12/28
Aldrighetti	Steroids	26/36	UD or US	PTC (intermittent)	52.4 (20–89)[d]	14/36
	Placebo	27/37			48 (20–78)[d]	12/36
Schmidt	Steroids	6/10	UD	None used	NA	NS
	Placebo	5/10			NA	NS
Hayashi	Steroids	11/102	NS	PTC (intermittent)	72 (0–247)[d]	NS
	Placebo	15/98			60 (0–203)[d]	NS

[a]Resection of three or more adjacent segments.
[b]The same method of vascular control used in both groups.
[c]Mean (SD).
[d]Median (range).
PTC, portal triad clamping; HVE, hemi-hepatic vascular occlusion; TVE, total vascular exclusion; NA, not applicable; NS, not stated; UD, ultrasonic dissector; KC, Kelly-clysis; US, ultrasonic shears.

Table 3 Indications for liver resection

	Steroid group	Placebo group
Hepatocellular carcinoma	92	87
Metastatic colorectal cancer	47	43
Cholangiocarcinoma	10	12
Living-related donor	4	4
Other	12	15

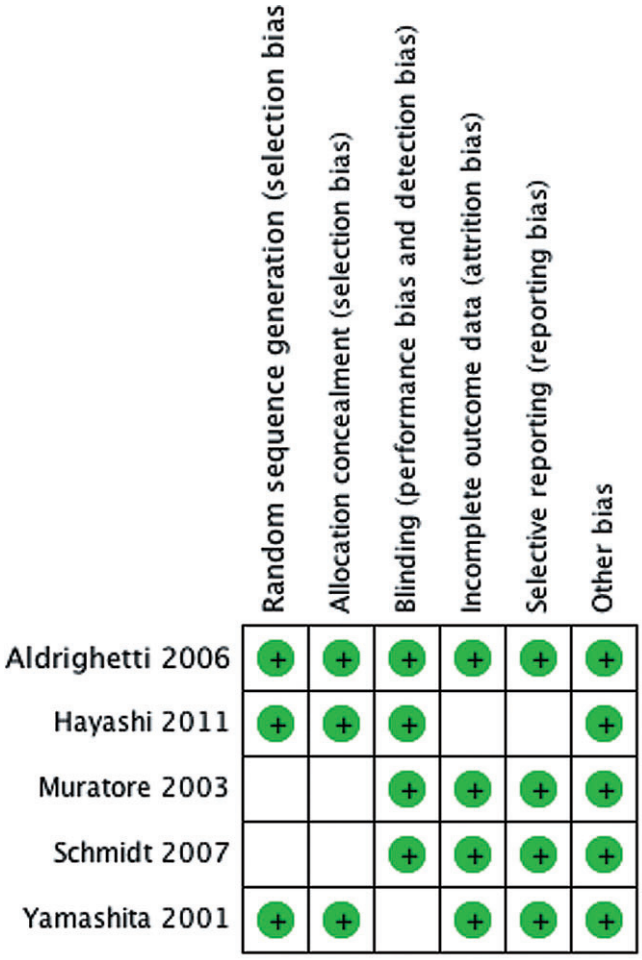

Figure 2 Risk of bias summary: review authors' judgements about each risk of bias item for each included study

PT (Fig. 3d). No effect was observed with respect to the length of stay ($P = 0.5$, OR = −0.99 95% CI −3.86 to 1.89). There was a statistically significant reduction in post-operative serum bilirubin associated with the use of steroids ($P = 0.05$, OR −0.43 95% CI −1.04 to −0.015). Steroid treatment was associated with a trend towards, although not statistically significant, reduced post-operative PT ($P = 0.1$, OR −0.04 95% CI −0.1 to 0.01). Data were available in four of the studies pertaining to post-operative serum IL-6 (Fig. 3e). There was a significant reduction in serum IL-6 in association with steroid administration ($P = 0.01$, OR −46.4 95% CI −83.4 to −9.39).

Discussion

This is the first systematic review of the use of pre-operative steroids focused exclusively on studies of liver resection. There were five RCT identified. Meta-analysis demonstrated reductions in the serum bilirubin and IL-6 on post-operative day one. There was a trend towards a reduction in the incidence of post-operative complications and PT, although this was not statistically significant. No effect was observed with respect to the length of stay.

One previous systematic review addressed different major abdominal procedures and found a decrease in length of stay and complications in those patients who were treated with pre-operative steroids.[33] Similarly, there has been one systematic review of the use of pre-operative steroids in oesophageal resection which suggested a similar benefit, but the authors did point out that the quality of the included trials was poor and this tempered the firmness with which conclusions could be drawn.[34] Additionally, there has been one systematic review of pharmacological interventions to reduce ischaemia–reperfusion injury in elective liver resection with vascular occlusion.[35] This review suggested that pre-operative steroids may attenuate such an injury.

Inflammation is necessary for tissue healing after surgery, but it is thought that an excessive response may contribute to post-operative morbidity, mortality and may delay post-operative recovery.[2,36–38] Additionally, an excessive inflammatory response may lead to SIRS and resultant multi-organ dysfunction syndrome.[39,40] The hepatic acute-phase response[41,42] is a physiological process believed to be focused on the restoration of homeostasis. This response is mainly modulated by inflammatory cytokines of which the most important appear to be IL-6, IL-8 and tumour necrosis factor alpha (TNF-a).[4,27,43,44] This systematic review included four studies in which IL-6 was measured. IL-6 was significantly decreased on post-operative day 1 after treatment with steroids.

There may be a relationship between the use of occlusive vascular control (such as portal triad clamping), extent of resection and the acute phase response to liver resection. Although the first animal studies showing a protective effect of steroids on liver ischaemia appeared more than 30 years ago,[45] the mechanism is still unclear. However, it may be related to suppression of inflammatory cytokines, increased tissue blood flow, stabilization of cell membranes and decreased lysosomal protease release.[21,46–50] The level of serum bilirubin on post operative day 1 does have a prognostic value in terms of clinical outcome and in particular the occurrence of liver failure.[51,52] Morbidity is related to the extent of resection as well as the ischaemic period. It may be that only a subset of high-risk patients (having a major resection or with prolonged vascular occlusion) are deriving benefit from pre-operative steroid administration. However, given the relatively

(a)

Study or Subgroup	Steroids Events	Steroids Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Aldrighetti 2006	5	36	14	37	14.6%	0.26 [0.08, 0.84]
Muratore 2003	7	25	12	28	14.7%	0.52 [0.16, 1.64]
Schmidt 2007	2	10	3	10	4.6%	0.58 [0.07, 4.56]
Hayashi 2011	41	102	42	98	61.6%	0.90 [0.51, 1.57]
Yamashita 2001	2	17	2	16	4.5%	0.93 [0.12, 7.55]
Total (95% CI)		**190**		**189**	**100.0%**	**0.68 [0.44, 1.06]**
Total events	57		73			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.81$, d.f. = 4 ($P = 0.43$); $I^2 = 0\%$
Test for overall effect: $Z = 1.72$ ($P = 0.09$)

Odds Ratio M-H, Random, 95% CI
0.05 0.2 1 5 20
Favours steriods Favours no steriods

(b)

Study or Subgroup	Steroids Mean	Steroids SD	Steroids Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Schmidt 2007	10.5	2	10	14.8	1.5	10	27.4%	-4.30 [-5.85, -2.75]
Aldrighetti 2006	6	4.25	36	8	8.5	37	22.2%	-2.00 [-5.07, 1.07]
Hayashi 2011	16.15	10.01	102	15.19	6.48	98	24.9%	0.96 [-1.37, 3.29]
Yamashita 2001	19.2	7.42	17	17.8	6.4	16	16.5%	1.40 [-3.32, 6.12]
Muratore 2003	13.4	19.1	25	11.6	7.5	28	9.0%	1.80 [-6.19, 9.79]
Total (95% CI)			**190**			**189**	**100.0%**	**-0.99 [-3.86, 1.89]**

Heterogeneity: $Tau^2 = 7.24$; $Chi^2 = 17.34$, d.f. = 4 ($P = 0.002$); $I^2 = 77\%$
Test for overall effect: $Z = 0.67$ ($P = 0.50$)

Mean Difference IV, Random, 95% CI
-10 -5 0 5 10
Favours steriods Favours no steriods

(c)

Study or Subgroup	Steroids Mean	Steroids SD	Steroids Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Aldrighetti 2006	1.39	0.6	36	2.8	1.2	37	22.0%	-1.41 [-1.84, -0.98]
Yamashita 2001	1.2	0.4	17	1.7	0.8	16	22.0%	-0.50 [-0.94, -0.06]
Hayashi 2011	0.89	0.37	102	1.11	0.64	98	25.6%	-0.22 [-0.37, -0.07]
Muratore 2003	0.9	0.7	25	1.1	2.2	28	15.1%	-0.20 [-1.06, 0.66]
Schmidt 2007	1.5	1.1	10	1.6	0.8	10	15.3%	-0.10 [-0.94, 0.74]
Total (95% CI)			**190**			**189**	**100.0%**	**-0.52 [-1.04, -0.01]**

Heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 26.94$, d.f. = 4 ($P < 0.0001$); $I^2 = 85\%$
Test for overall effect: $Z = 1.99$ ($P = 0.05$)

Mean Difference IV, Random, 95% CI
-2 -1 0 1 2
Favours steriods Favours no steriods

(d)

Study or Subgroup	Steroids Mean	Steroids SD	Steroids Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Aldrighetti 2006	1.1	0.11	36	1.2	0.15	37	21.7%	-0.10 [-0.16, -0.04]
Yamashita 2001	1.48	0.14	17	1.56	0.14	16	15.3%	-0.08 [-0.18, 0.02]
Hayashi 2011	1.16	0.08	102	1.22	0.09	98	28.4%	-0.06 [-0.08, -0.04]
Schmidt 2007	1.27	0.09	10	1.3	0.19	10	10.7%	-0.03 [-0.16, 0.10]
Muratore 2003	1.05	0.1	25	1.01	0.08	28	23.9%	0.04 [-0.01, 0.09]
Total (95% CI)			**190**			**189**	**100.0%**	**-0.04 [-0.10, 0.01]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 16.67$, d.f. = 4 ($P = 0.002$); $I^2 = 76\%$
Test for overall effect: $Z = 1.64$ ($P = 0.10$)

Mean Difference IV, Random, 95% CI
-0.2 -0.1 0 0.1 0.2
Favours steriods Favours no steriods

(e)

Study or Subgroup	Steroids Mean	Steroids SD	Steroids Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Hayashi 2011	65.6	82.9	102	141.7	113.3	98	25.2%	-76.10 [-103.70, -48.50]
Schmidt 2007	16.2	13.5	10	91.5	85.5	10	18.1%	-75.30 [-128.95, -21.65]
Aldrighetti 2006	26	20	36	73	38	37	28.2%	-47.00 [-60.88, -33.12]
Muratore 2003	16.3	19.1	25	17.4	24.5	28	28.5%	-1.10 [-12.86, 10.66]
Total (95% CI)			**173**			**173**	**100.0%**	**-46.40 [-83.40, -9.39]**

Heterogeneity: $Tau^2 = 1215.54$; $Chi^2 = 41.86$, d.f. = 3 ($P < 0.00001$); $I^2 = 93\%$
Test for overall effect: $Z = 2.46$ ($P = 0.01$)

Mean Difference IV, Random, 95% CI
-100 -50 0 50 100
Favours Steroids Favours control

Figure 3 Forest plots illustrating meta-analysis of outcomes in patients undergoing a liver resection with pre-operative steroid administration (steroids) or placebo (control). The outcomes analysed were post-operative complications (a), length of stay (b), serum bilirubin (c), prothrombin time (d) and IL-6 on postoperative day 1 (e). M-H, Mantel-Haenszel; 95% CI, 95% confidence

small size of each of the studies in this review, there is insufficient data to resolve this question.

Although pre-operative steroids have been recommended for liver resection by some authors,[53] there have been concerns about the effect this may have on post-operative liver regeneration. Liver regeneration involves a number of steps, but IL-6 and TNF-a are important initiators of the process.[54–56] As we have concluded steroids decrease the levels of IL-6 and this could theoretically impair liver regeneration. However, it has been shown that overproduction of IL-6 may also inhibit liver regeneration and as such, steroid administration may have a positive effect.[57] Glanemann *et al.*[47] showed in an animal model that steroids had no effect on liver regeneration. It is also important to note that although we have demonstrated that IL-6 is suppressed by steroid administration, it is not completely abolished.

Another concern with steroid administration is the potential increased risk of infectious complications. This concern is not substantiated by the data from this meta-analysis. Steroid administration may in fact reduce the incidence of infectious complications. The mechanisms for this apparently paradoxical effect are not clear. However, there are a number of candidate mediators including immunosuppressive acidic protein (IAP) and candida antigen. IAP is a glycoprotein,[58] levels of which are significantly increased by complex surgery[59] and may correlate with post-operative infections.[60] Similarly, candida antigen has been shown to be associated with an increase in infectious complications after a hepatectomy.[61] Yamashita *et al.*[21] showed a decrease in the levels of these two markers with steroid administration. Human leukocyte antigen (HLA)-DR expression on peripheral monocytes has been shown to correlate with an increased risk of infection after major surgery.[62] Schmidt *et al.*[24] found no evidence of an increase in HLA-DR expression, or of a decrease in cellular immunity in the group of patients treated with steroids.

In all five of the studies included in this analysis, the steroid administration regime was slightly different. However the regimes did have common features of pre-operative administration and the use of methylprednisolone. Corticosteroids are known to be less effective or indeed ineffectual if given after induction of the inflammatory response.[63,64] Given that there is a delay to the onset of the anti-inflammatory effects of steroids for 1 to 2 h after administration,[14] all studies gave steroids pre-operatively. Methylprednisolone was used in all of the studies as its anti-inflammatory actions are five times as strong as cortisol with less effect on electrolyte metabolism.[65] The half life of methylprednisolone in the blood is 2.8 h and its biological action is prolonged for up to 36 h after administration.[65] Therefore it seems reasonable that a single dose of 500 mg would be sufficient to suppress both early and late inflammatory effects.[23,66] This variation may account for some of the heterogeneity observed in the meta-analysis.

There are some weaknesses in this meta-analysis. The analysis includes only RCT; however, they are of differing quality, providing variable information about potential sources of bias. Because the number of trials in the analysis is small, publication bias cannot be reliably assessed. Meta-analysis is primarily a means for addressing the issue of inadequate statistical power in studies with a small sample size.[67] Given that there was a non-statistically significant trend in many outcomes between the steroid and placebo groups, the question naturally arises whether this is a result of a lack of power or could be a false-negative result owing to other causes. There was highly significant heterogeneity in the length of stay, bilirubin and PT on post-operative day one. This heterogeneity may be attributable to differences in the patients (such as underlying liver disease), intervention (dose of steroids), operations (extent of liver resection and use of vascular occlusion), outcome assessment and quality of reporting. This heterogeneity may obscure an important treatment effect.

More than half of the patients came from one study where the steroid-treated group was given larger doses and administration was continued over a number of days. From a western perspective, the patient cohort was different in that nearly half of the patients were having a resection for hepatocellular carcinoma. In most western series, the majority of patients will be having a resection for colorectal liver metastases and there will also be confounding issues related to chemotherapy-induced liver damage. In spite of these weaknesses, there does seem to be a clear benefit or trend towards a benefit in every parameter examined (except length of stay). Although the evidence is so far insufficient to justify recommending a change in routine clinical practice, there is a need for a larger multi-centre trial to further explore this strategy.

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Conflicts of interest

None declared.

References

1. Faist E, Schinkel C, Zimmer S. (1996) Update on the mechanisms of immune suppression of injury and immune modulation. *World J Surg* 20:454–459.
2. Hill AG. (2000) Initiators and propagators of the metabolic response to injury. *World J Surg* 24:624–629.
3. Robertson CM, Coopersmith CM. (2006) The systemic inflammatory response syndrome. *Microbes Infect* 8:1382–1389.
4. Biffl WL, Moore EE, Moore FA, Peterson VM. (1996) Interleukin-6 in the injured patient. Marker of injury or mediator of inflammation? *Ann Surg* 224:647–664.
5. Kehlet H, Dahl JB. (2003) Anaesthesia, surgery, and challenges in post-operative recovery. *Lancet* 362:1921–1928.
6. Sato N, Koeda K, Ikeda K, Kimura Y, Aoki K, Iwaya T *et al*. (2002) Randomized study of the benefits of preoperative corticosteroid administration on the postoperative morbidity and cytokine response in patients undergoing surgery for esophageal cancer. *Ann Surg* 236:184–190.

7. Jerin A, Pozar-Lukanovic N, Sojar V, Stanisavljevic D, Paver-Erzen V, Osredkar J. (2003) Balance of pro- and anti-inflammatory cytokines in liver surgery. *Clin Chem Lab Med* 41:899–903.
8. Teoh NC, Farrell GC. (2003) Hepatic ischemia reperfusion injury: pathogenic mechanisms and basis for hepatoprotection. *J Gastroenterol Hepatol* 18:891–902.
9. Badia JM, Ayton LC, Evans TJ, Carpenter AJ, Nawfal G, Kinderman H *et al*. (1998) Systemic cytokine response to hepatic resections under total vascular exclusion. *Eur J Surg* 164:185–190.
10. Kehlet H. (2007) Glucocorticoids for peri-operative analgesia: how far are we from general recommendations? *Acta Anaesthesiol Scand* 51:1133–1135.
11. Fukami Y, Terasaki M, Okamoto Y, Sakaguchi K, Murata T, Ohkubo M *et al*. (2009) Efficacy of preoperative dexamethasone in patients with laparoscopic cholecystectomy: a prospective randomized double-blind study. *J Hepatobiliary Pancreat Surg* 16:367–371.
12. Feo CV, Sortini D, Ragazzi R, De Palma M, Liboni A. (2006) Randomized clinical trial of the effect of preoperative dexamethasone on nausea and vomiting after laparoscopic cholecystectomy. *Br J Surg* 93:295–299.
13. Gan TJ, Meyer TA, Apfel CC, Chung F, Davis PJ, Habib AS *et al*. (2007) Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 105:1615–1628.
14. Holte K, Kehlet H. (2002) Perioperative single-dose glucocorticoid administration: pathophysiologic effects and clinical implications. *J Am Coll Surg* 195:694–712.
15. Saidi RF, Chang J, Verb S, Brooks S, Nalbantoglu I, Adsay V *et al*. (2007) The effect of methylprednisolone on warm ischemia-reperfusion injury in the liver. *Am J Surg* 193:345–347; discussion 347–348.
16. Santiago Delpin EA, Figueroa I, Lopez R, Vazquez J. (1975) Protective effect of steroids on liver ischemia. *Am Surg* 41:683–685.
17. Alegre ML, Vandenabeele P, Depierreux M, Florquin S, Deschodt-Lanckman M, Flamand V *et al*. (1991) Cytokine release syndrome induced by the 145-2C11 anti-CD3 monoclonal antibody in mice: prevention by high doses of methylprednisolone. *J Immunol* 146:1184–1191.
18. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP *et al*. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 62:e1–34.
19. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD *et al*. (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343:d5928.
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. (2003) Measuring inconsistency in meta-analyses. *BMJ* 327:557–560.
21. Yamashita Y, Shimada M, Hamatsu T, Rikimaru T, Tanaka S, Shirabe K *et al*. (2001) Effects of preoperative steroid administration on surgical stress in hepatic resection: prospective randomized trial. *Arch Surg* 136:328–333.
22. Muratore A, Ribero D, Ferrero A, Bergero R, Capussotti L. (2003) Prospective randomized study of steroids in the prevention of ischaemic injury during hepatic resection with pedicle clamping. *Br J Surg* 90:17–22.
23. Aldrighetti L, Pulitano C, Arru M, Finazzi R, Catena M, Soldini L *et al*. (2006) Impact of preoperative steroids administration on ischemia-reperfusion injury and systemic responses in liver surgery: a prospective randomized study. *Liver Transpl* 12:941–949.
24. Schmidt SC, Hamann S, Langrehr JM, Hoflich C, Mittler J, Jacob D *et al*. (2007) Preoperative high-dose steroid administration attenuates the surgical stress response following liver resection: results of a prospective randomized study. *J Hepatobiliary Pancreat Surg* 14:484–492.
25. Hayashi Y, Takayama T, Yamazaki S, Moriguchi M, Ohkubo T, Nakayama H *et al*. (2011) Validation of perioperative steroids administration in liver resection: a randomized controlled trial. *Ann Surg* 253:50–55.
26. Pulitano C, Aldrighetti L, Arru M, Finazzi R, Soldini L, Catena M *et al*. (2007) Prospective randomized study of the benefits of preoperative corticosteroid administration on hepatic ischemia-reperfusion injury and cytokine response in patients undergoing hepatic resection. *HPB* 9:183–189.
27. Pulitano C, Aldrighetti L, Arru M, Finazzi R, Catena M, Guzzetti E *et al*. (2007) Preoperative methylprednisolone administration maintains coagulation homeostasis in patients undergoing liver resection: importance of inflammatory cytokine modulation. *Shock* 28:401–405.
28. Turner S, Dhamarajah S, Bosomworth M, Bellamy MC. (2006) Effect of perioperative steroids on renal function after liver transplantation. *Anaesthesia* 61:253–259.
29. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L *et al*. (2011) Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. *Surgery* 149:680–688.
30. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R *et al*. (2011) Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery* 149:713–724.
31. Rahbari NN, Garden OJ, Padbury R, Maddern G, Koch M, Hugh TJ *et al*. (2011) Post-hepatectomy haemorrhage: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *HPB* 13:528–535.
32. Dindo D, Demartines N, Clavien PA. (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 240:205–213.
33. Srinivasa S, Kahokehr AA, Yu TC, Hill AG. (2011) Preoperative glucocorticoid use in major abdominal surgery: systematic review and meta-analysis of randomized trials. *Ann Surg* 254:183–191.
34. Engelman E, Maeyens C. (2010) Effect of preoperative single-dose corticosteroid administration on postoperative morbidity following esophagectomy. *J Gastrointest Surg* 14:788–804.
35. Abu-Amara M, Gurusamy K, Hori S, Glantzounis G, Fuller B, Davidson BR. (2010) Systematic review of randomized controlled trials of pharmacological interventions to reduce ischaemia-reperfusion injury in elective liver resection with vascular occlusion. *HPB* 12:4–14.
36. Wilmore DW. (2000) Metabolic response to severe surgical illness: overview. *World J Surg* 24:705–711.
37. Desborough JP. (2000) The stress response to trauma and surgery. *Br J Anaesth* 85:109–117.
38. Zargar-Shoshtari K, Hill AG. (2009) Postoperative fatigue: a review. *World J Surg* 33:738–745.
39. Davies MG, Hagen PO. (1997) Systemic inflammatory response syndrome. *Br J Surg* 84:920–935.
40. Nystrom PO. (1998) The systemic inflammatory response syndrome: definitions and aetiology. *J Antimicrob Chemother* 41 (Suppl. A):1–7.
41. Ramadori G, Christ B. (1999) Cytokines and the hepatic acute-phase response. *Semin Liver Dis* 19:141–155.
42. Moshage H. (1997) Cytokines and the hepatic acute phase response. *J Pathol* 181:257–266.
43. Biffl WL, Moore EE, Moore FA, Barnett CC, Jr, Carl VS, Peterson VN. (1996) Interleukin-6 delays neutrophil apoptosis. *Arch Surg* 131:24–29; discussion 29–30.

44. van der Poll T, Buller HR, ten Cate H, Wortel CH, Bauer KA, van Deventer SJ *et al*. (1990) Activation of coagulation after administration of tumor necrosis factor to normal subjects. *N Engl J Med* 322:1622–1627.

45. Figueroa I, Santiago-Delpin EA. (1975) Steroid protection of the liver during experimental eschemia. *Surg Gynecol Obstet* 140:368–370.

46. Fujioka T, Murakami M, Niiya T, Aoki T, Murai N, Enami Y *et al*. (2001) Effect of methylprednisolone on the kinetics of cytokines and liver function of regenerating liver in rats. *Hepatol Res* 19:60–73.

47. Glanemann M, Strenziok R, Kuntze R, Munchow S, Dikopoulos N, Lippek F *et al*. (2004) Ischemic preconditioning and methylprednisolone both equally reduce hepatic ischemia/reperfusion injury. *Surgery* 135:203–214.

48. Wang M, Sakon M, Umeshita K, Okuyama M, Shiozaki K, Nagano H *et al*. (2001) Prednisolone suppresses ischemia-reperfusion injury of the rat liver by reducing cytokine production and calpain mu activation. *J Hepatol* 34:278–283.

49. Chiappa AC, Makuuchi M, Zbar AP, Biella F, Vezzoni A, Torzilli G *et al*. (2004) Protective effect of methylprednisolone and of intermittent hepatic pedicle clamping during liver vascular inflow occlusion in the rat. *Hepatogastroenterology* 51:1439–1444.

50. Nagy P, Kiss A, Schnur J, Thorgeirsson SS. (1998) Dexamethasone inhibits the proliferation of hepatocytes and oval cells but not bile duct cells in rat liver. *Hepatology* 28:423–429.

51. Balzan S, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D *et al*. (2005) The '50-50 criteria' on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann Surg* 242:824–828; discussion 828–829.

52. Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S *et al*. (2007) Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. *J Am Coll Surg* 204:854–862; discussion 862–864.

53. Torzilli G, Makuuchi M, Inoue K, Takayama T, Sakamoto Y, Sugawara Y *et al*. (1999) No-mortality liver resection for hepatocellular carcinoma in cirrhotic and noncirrhotic patients: is there a way? A prospective analysis of our approach. *Arch Surg* 134:984–992.

54. Fausto N. (2000) Liver regeneration. *J Hepatol* 32 (1 Suppl.):19–31.

55. Mangnall D, Bird NC, Majeed AW. (2003) The molecular physiology of liver regeneration following partial hepatectomy. *Liver Int* 23:124–138.

56. Streetz KL, Luedde T, Manns MP, Trautwein C. (2000) Interleukin 6 and liver regeneration. *Gut* 47:309–312.

57. Wustefeld T, Rakemann T, Kubicka S, Manns MP, Trautwein C. (2000) Hyperstimulation with interleukin 6 inhibits cell cycle progression after hepatectomy in mice. *Hepatology* 32:514–522.

58. Shibata Y, Tamura K, Ishida N. (1983) In vivo analysis of the suppressive effects of immunosuppressive acidic protein, a type of alpha 1-acid glycoprotein, in connection with its high level in tumor-bearing mice. *Cancer Res* 43:2889–2896.

59. Takenoshita S, Hashizume T, Asao T, Nakamura J, Tsukada K, Katoh R *et al*. (1994) Influence of surgical insults for colorectal cancers on neuroendocrine and immune parameters. *Oncol Rep* 1:1029–1033.

60. Takenoshita S, Tsukada K, Nakamura J, Shitara Y, Asao T, Kato R *et al*. (1996) Immunosuppressive acidic protein (IAP) level in serum and peritoneal washings, and its implication in determining multidisciplinary treatments. *Anticancer Res* 16 (4B):2269–2272.

61. Shirabe K, Takenaka K, Yamatomto K, Kawahara N, Itasaka H, Nishizaki T *et al*. (1997) Impaired systemic immunity and frequent infection in patients with Candida antigen after hepatectomy. *Hepatogastroenterology* 44:199–204.

62. Buunen M, Gholghesaei M, Veldkamp R, Meijer DW, Bonjer HJ, Bouvy ND. (2004) Stress response to laparoscopic surgery: a review. *Surg Endosc* 18:1022–1028.

63. Guirao X, Lowry SF. (1996) Biologic control of injury and inflammation: much more than too little or too late. *World J Surg* 20:437–446.

64. Pearce D, Yamamoto KR. (1993) Mineralocorticoid and glucocorticoid receptor activities distinguished by nonreceptor factors at a composite response element. *Science* 259:1161–1165.

65. Stubbs SS. (1975) Corticosteroids and bioavailability. *Transplant Proc* 7:11–19.

66. Serracino-Inglott F, Habib NA, Mathie RT. (2001) Hepatic ischemia-reperfusion injury. *Am J Surg* 181:160–166.

67. O'Rourke K. (2007) An historical perspective on meta-analysis: dealing quantitatively with varying study results. *J R Soc Med* 100:579–582.