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Original articles

Preoperative high-dose steroid administration attenuates the surgical stress response following liver resection: results of a prospective randomized study

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Abstract
Background/Purpose. Major abdominal surgery such as liver resection is associated with an excessive hyperinflammatory response and transient immunosuppression. We investigated the immunomodulating effect of preoperative pulse administration of high-dose methylprednisolone in patients undergoing hepatic resection without pedicle clamping.
Methods. Twenty patients who underwent hepatic resection were randomized into two groups: a steroid group ($n = 10$), in which patients were given 30 mg/kg per body weight (BW) methylprednisolone intravenously, and a control group ($n = 10$), in which patients received a placebo (sodium chloride) infusion. The main outcome parameter to assess systemic stress was the serum plasma level of interleukin-6 (IL-6). To evaluate cell-mediated immune function, human leukocyte antigen-DR (HLA-DR) expression on peripheral blood monocytes and lipopolysaccharide (LPS)-induced tumor necrosis factor-α (TNF-α) release by peripheral monocytes was measured. Other investigated serum parameters included C-reactive protein (CRP), total bilirubin, alanine aminotransferase (ALT), prothrombin time (PT)-INR, and cytokines such as IL-8 and IL-10 and TNF-α. Postoperative convalescence, complication rate, and length of hospital stay were compared between the groups.
Results. Postoperative plasma concentrations of IL-6 (days 1 and 2), IL-8 (days 2 and 3), and CRP (days 1–4) were significantly lower in the steroid than in the control group. The total bilirubin concentration was significantly lower on day 6 in the steroid than in the control group. Four hours after surgery, LPS-induced TNF-α secretion was significantly reduced in the steroid group, but it increased rapidly during the following days. HLA-DR, ALT, and PT-INR levels were not different between the two groups. The postoperative hospital stay in the steroid group was significantly lower compared to that in the control group (mean, 10.5 days versus 14.8 days; $P < 0.05$). No differences were found in the convalescence score or postoperative complication rate.
Conclusions. Intravenous methylprednisolone administration before hepatic resection significantly reduced systemic inflammatory cytokine release. No adverse effect on immunity was noted due to the methylprednisolone. We found no significant difference in the convalescence score, but a significantly shorter hospital stay in the steroid group. Further studies with more patients are needed to elucidate the clinical impact of preoperative steroid bolus therapy in liver surgery.

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Introduction

Major abdominal surgery leads to an acute inflammatory response, which is characterized by hemodynamic and metabolic alterations, with the production and release of various chemical mediators, including stress hormones, free radicals, and cytokines.[1] Physiologically, surgical trauma induces inflammatory responses and assists in activating the host defense system to resist infections, and maintain postoperative organ perfusion and homeostasis. The immediate hyperactivation of the immune system in response to the tissue injury is followed by transient immunosuppression, leading to an increased susceptibility for the development of postoperative septic complications.[1,2] In the acute phase following abdominal surgery, proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL) 1-β, and IL-6 play an important role in surgical stress reactions by directly influencing systemic cell-mediated immunity and the local inflammatory reaction.[3] While a balance of pro- and anti-inflammatory cytokines is essential for the patient's appropriate immune response, the postoperative overproduction of proinflammatory cytokines may lead to tissue damage via the production of free oxygen species and may also result in systemic inflammatory response syndrome (SIRS) with subsequent multiorgan failure.[4] In addition to the tissue trauma associated with abdominal surgery, liver resection itself may enhance the production and release of cytokines, especially when the Pringle maneuver is used.[5,6] To attenuate the postoperative inflammatory response in hepatic surgery, perioperative administration of steroids has been suggested when utilizing the Pringle maneuver.[7–10] However, due to the massive concentration of macrophages (Kupffer cells) in the liver tissue, an exaggerated cytokine response following hepatic surgery without pedicle clamping can be suggested. The aim of the present prospective randomized trial was to evaluate the effect and the safety of preoperative high-dose methylprednisolone (MP) administration in liver surgery without portal triad clamping on the postoperative immune response and the postoperative clinical course.

Patients and methods

Hypothesis, endpoints, and sample-size calculation

The null hypothesis (H_0) of the analyzed data showed that the IL-6 response did not differ in the control and the steroid groups. The alternative hypothesis (H_A) was that the postoperative plasma concentration of IL-6 differs between the steroid and the control group. Minor endpoints included the postoperative plasma levels of IL-8, IL-10, TNF-α, human leukocyte antigen-DR (HLA-DR) receptor expression on peripheral monocytes, lipopolysaccharide (LPS)-induced TNF-α, and C-reactive protein (CRP). Clinical endpoints were postoperative complications, convalescence, and length of hospital stay. With a hypothesized difference of 80% of the postoperative plasma level of IL-6 between the steroid and the control groups, the calculated sample size was ten patients in each group, with $\alpha = 0.05$, and $\beta = 0.2$ (power, 80%).

Study population

The study was approved by the local ethics committee. All patients gave their informed consent prior to enrolment in the study. Twenty patients undergoing hepatic resection were included in the study. Randomization of patients to either the steroid or the control group was performed in a double-blind manner. Exclusion criteria were: liver cirrhosis, endocrine disorders, immunopathies, coagulopathies, ulcus ventriculi/duodeni, obesity (body mass index >32 kg/m^2), osteoporosis, glaucoma, and American Society of Anesthesiologists physical status (ASA) more than III.

Perioperative management

Patients in the steroid group received 30 mg/kg per BW of MP intravenously 90 min before surgery, and patients in the control group received 50 ml physiologic saline intravenously.

All hepatic resections were performed without the Pringle maneuver. Transection of the liver parenchyma was done with an ultrasound dissector (CUSA; Tyco Healthcare, Mansfield, MA, USA). Small vessels or bile ducts were controlled by clips or ligations. Intraoperative systemic single-shot antibiotics (second-generation cephalosporin and metronidazole) were routinely applied in all patients.

Blood sampling and cytokine analysis

Venous blood was drawn from each patient preoperatively, 4 h after surgery and on the first, second, third, and seventh postoperative days (PODs). Blood samples for cytokine analysis were drawn into two 2.7-ml monovettes containing ethylenediamine tetraacetic acid (EDTA)/aprotinin and two 5.5-ml monovettes containing lithium/heparin. The plasma was centrifuged and stored frozen at −80 ºC for later analysis. For the measurement of TNF-α, IL-6, IL-8, and IL-10, we used a semi-automated enzyme-linked immunosorbent assay (ELISA) system (Immulite; DPC Biermann, Bad Nauheim, Germany).

LPS whole-blood test

For the measurement of LPS-induced TNF-α production, we used a commercially available whole-blood test (DPC Biermann). Fifty microliters of heparinized blood was suspended in 500 µl RPMI medium containing 500 pg/ml LPS, and incubation was done at 37 ºC/5% CO2 for 4 h. After gentle mixing, the supernatant was collected by centrifugation (1000 *g*, 5 min) and stored at −80 ºC until measurement of TNF-α.

Quantification of monocytic HLA-DR expression

Monocytic HLA-DR expression was quantified flow-cytometrically as recently described.[11]

CRP, aspartate aminotransferase (AST), ALT, total bilirubin, and prothrombin time (PT)-INR were determined using commercially available reaction kits at the Institute of Laboratory Medicine, Charité Campus Virchow Clinic, University Medicine Berlin.

Assessment of convalescence

Convalescence was assessed by the mobilization score described by Nagelschmidt et al.[6] (Table 1). The assessment started 1 day before the operation, and was documented daily until the patient was discharged.

Table 1. Mobilization score as described by Nagelschmidt et al.[6]

Parameter	Score
Fluid intake	
Drinks without help	0
Drinks but needs intravenous supplementation	–1
Intravenous infusion only	–2
Food intake	
Eats without help	0
Eats with help	–1
Parenteral nutrition/enteral nutrition via gastric tube	–2
Washing	
Washes out of bed	0
Washes in bed	–1
Needs bed wash	–2
Bowel and bladder function	
Continent and independent	0
Needs bedpan	–1
No stool/incontinent	–2
Mobility	
Fully mobile	0
Partly mobile	–1
Immobile	–2
Mental needs	
Needs little psychological support	0
Needs some psychological support	–1
Needs a lot of psychological support	–2
Total score points	0 to –12

Statistical analysis

Statistical analysis was done with the Statistical Package for Social Sciences (SPSS 12.0; Chicago, IL, USA). Continuous variables were compared by the Mann-Whitney *U*-test and categorical parameters by the χ^2 or Fisher exact-test. Differences were considered to be significant at a level of 5% ($P < 0.05$).

Results

Twenty patients fulfilled the inclusion criteria and were randomly assigned to receive either high-dose MP (n = 10) or placebo (n = 10) prior to hepatic resection. The preoperative clinical and laboratory variables and the extent of resection are summarized in Table 2.

Surgical complications

During the postoperative course, one patient from the steroid group and one from the control group developed a biliary stenosis associated with a small leakage after right (steroid group) and left (control group) hemihepatectomy. Both patients were successfully treated by endoscopic stenting and sphincterotomy. The patient in the control group with the biliary stenosis

Table 2. Comparison of perioperative parameters between the control and steroid groups

Variable	Control group (n = 10)	Steroid group (n = 10)	P
Age (years)	65	57	<0.05
Sex ratio (M : W)	4 : 6	3 : 7	0.64
Diagnosis			
Metastastic liver tumor	4	4	
Hepatocellular carcinoma	1	2	
Cholangiocellular carcinoma	2	0	
Benign diseases	3	4	
Intraoperative variables			
Operative procedures			
Segment II/III resection	5	4	
Segment V–VIII resection	5	6	
Blood loss (ml)[a]	780	340	0.51
Operative time (min)	252	222	0.24
Preoperative blood chemistry			
AST (U/l)[a]	21 ± 10.9	37 ± 24.9	0.14
ALT (U/l)[a]	19 ± 14.3	21 ± 15.3	0.63
Bilirubin (mg/dl)[a]	0.5 ± 0.3	0.6 ± 0.3	0.23
Postoperative blood chemistry			
AST (U/l)[a] peak	247 ± 180.0	280 ± 120.9	0.45
ALT (U/l)[a] peak	242 ± 165.7	238 ± 113.0	0.68
Bilirubin (mg/dl)[a] POD 1	1.6 ± 0.8	1.5 ± 1.1	0.59
Prothrombin time-INR POD 1	1.3 ± 0.19	1.27 ± 0.09	0.45
Postoperative complications			
Bile leakage	1	1	
Biliary stenosis	1	1	
Wound infection	1	0	

AST, aspartate aminotransferase; ALT, alanine aminotransferase; POD, postoperative day

[a] Values are means (SD)

additionally developed a deep wound abscess. The hospital stay of these two patients was prolonged, at 33 days (control group) and 13 days (steroid group).

Humoral and cellular stress responses

Analysis of the plasma concentration of IL-6 demonstrated a peak in both groups 4 h after surgery, with a subsequent decline. Mean (SD) IL-6 levels were significantly lower in the steroid than in the control group on POD 1 (16.19 ± 13.50 pg/ml vs 91.46 ± 85.49 pg/ml; P = 0.008) and on POD2 (13.71 ± 12.84 pg/ml vs 76.68 ± 73.34 pg/ml; P = 0.002; Fig. 1). Mean (SD) levels of IL-8 were significantly suppressed in the steroid group compared to the control group on POD 2 (10.61 ± 17.74 pg/ml vs 19.19 ± 14.73 pg/ml; P = 0.008) and on POD 3 (5.00 ± 0.00 pg/ml vs 12.24 ± 12.83 pg/ml; P = 0.005). In the steroid group, the mean (SD) plasma level of IL-10 reached a peak 4 h after surgery (19.70 ± 22.94 pg/ml vs 8.79 ± 6.80 pg/ml), followed by a continuous decrease during the following days. The postoperative IL-10 values in the control group were higher than those in the steroid group; however the differences were not significant. The postoperative plasma concentrations of TNF-α were lower in the steroid group than in the control group, but were not significantly different (Fig. 2).

The analysis of HLA-DR expression demonstrated postoperative suppression in both groups; however, the values were not significantly different between the steroid and the control groups (Fig. 3a). In the steroid group, LPS-induced TNF-α secretion was significantly suppressed at 4 h after surgery, followed by a rapid increase (Fig. 3b).

There was an increase in the plasma concentration of CRP in both groups following surgery. The mean (SD) CRP levels were significantly higher in the control group than in the steroid group on POD 1 (4.5 ± 1.77 mg/dl vs 3.0 ± 1.43 mg/dl; P = 0.043), POD 2 (10.2 ± 5.32 mg/dl vs 3.3 ± 1.81 mg/dl; P = 0.002), POD 3 (11.0 ± 5.06 mg/dl vs 2.6 ± 1.57 mg/dl; P = 0.001), and POD 4 (9.5 ± 4.34 mg/dl vs 3.5 ± 1.17 mg/dl; P = 0.014; Fig. 4). The mean (SD) total bilirubin level on POD 6 was significantly higher in the control group than in the steroid group (1.6 ± 0.33 mg/dl vs 1.0 ± 0.26 mg/dl; P = 0.033). No significant differences were found in ALT levels (Fig. 5, Table 2) or PT-INR (Table 2).

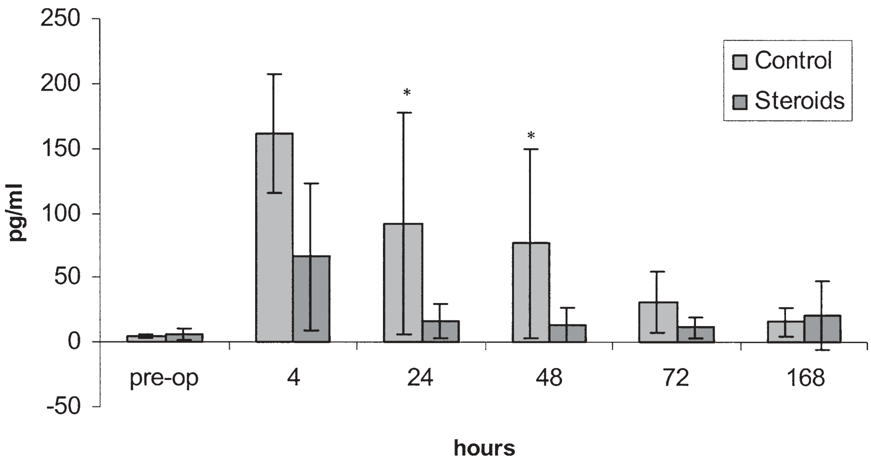


Fig. 1. Comparison of postoperative serum interleukin 6 levels. Data are expressed as means ± SD. *Asterisk* indicates $P < 0.05$

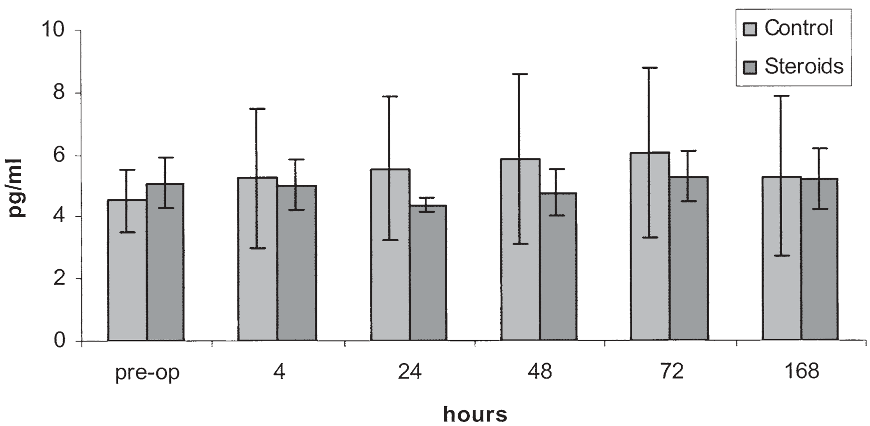
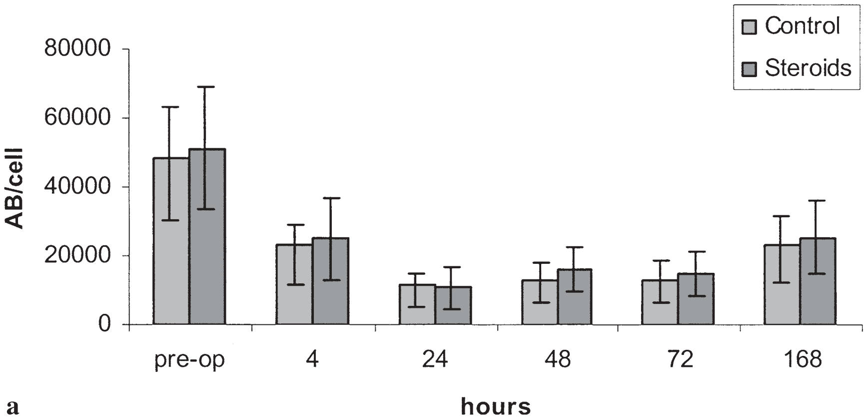
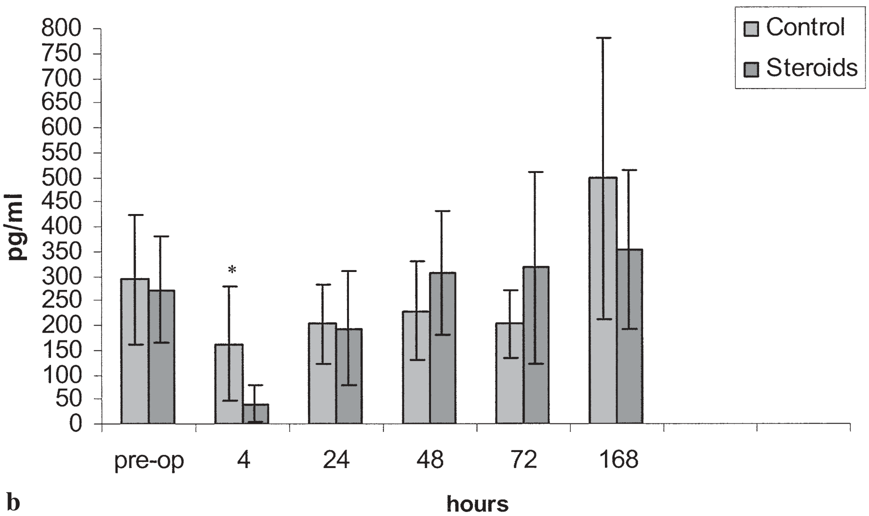


Fig. 2. Comparison of postoperative serum tumor necrosis factor (TNF)-α. Data are expressed as means ± SD



a



b

Fig. 3. **a** Comparison of postoperative human leukocyte antigen-DR (HLA-DR) expression. Data are expressed as means ±SD **b.** Comparison of postoperative lipopolysaccharide (LPS)-induced TNF-α. on peripheral monocytes. Data are expressed as means ±SD. *Asterisk* indicates $P < 0.05$

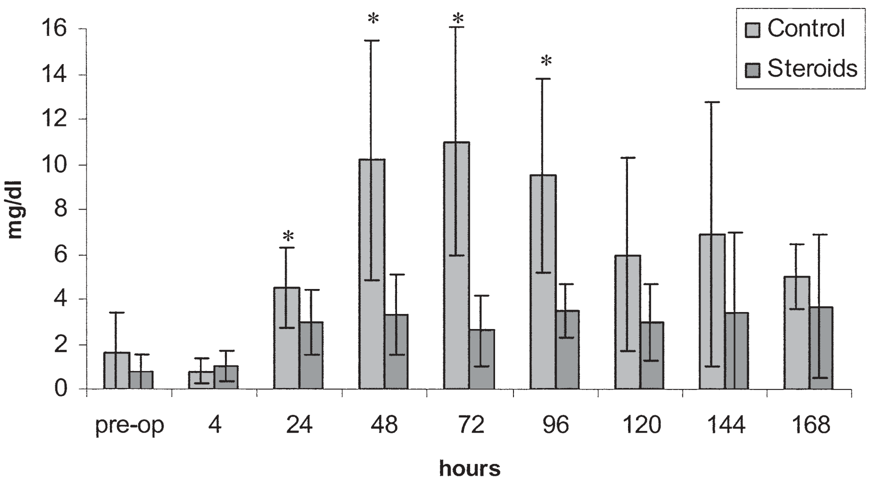


Fig. 4. Comparison of postoperative serum C-reactive protein (CRP) levels. Data are expressed as means ±SD. *Asterisk* indicates $P < 0.05$

Convalescence and hospital stay

After an immediate drop until POD 2, the convalescence score demonstrated improved values on the following days in both groups, without significant differences (Fig. 6). Comparison of the postoperative hospital stay showed that the patients in the steroid group were discharged significantly earlier, after a mean of 10.5 days (range, 7–15 days) compared with 14.8 days (range, 10–16 days) in the control group ($P < 0.05$).

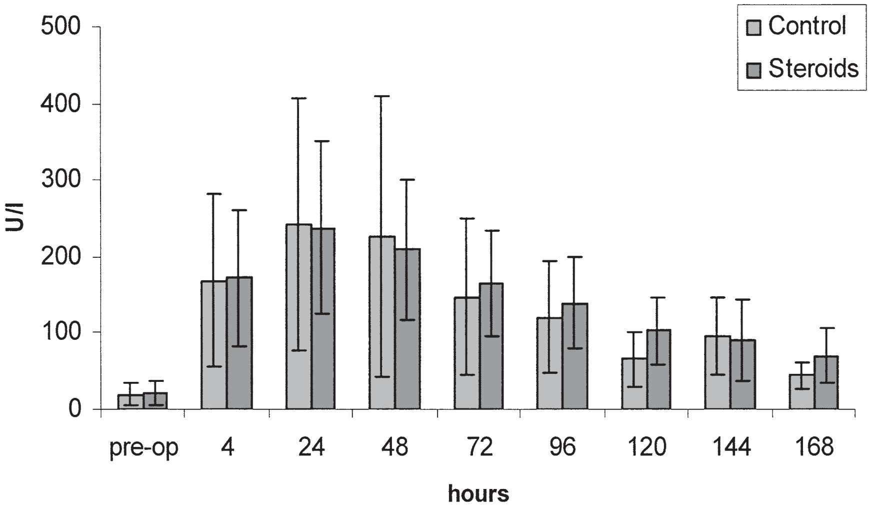


Fig. 5. Comparison of postoperative serum alanine aminotransferase (ALT). Data are expressed as means ± SD

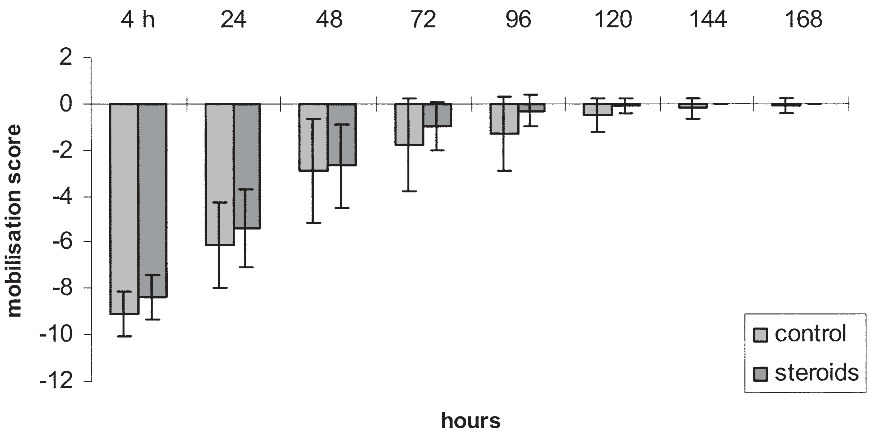


Fig. 6. Comparison of postoperative convalescence. Data are expressed as means ± SD

Discussion

Apart from metabolic and endocrinologic alterations, the postoperative inflammatory response includes the local release of cytokines from stimulated macrophages and monocytes.[12] Cytokines are important mediators of the inflammatory response, and they influence both specific and nonspecific pathways of the cellular and humoral immune system.[13] The released cytokines activate the production of other cytokines, a process that results in a cytokine cascade consisting of pro- and anti-inflammatory cytokines. In the acute-phase response, the cytokines TNF-α and IL-6 play a key role as modulators of the inflammation.[13] TNF-α belongs to the first released cytokines in the acute phase and is one of the most potent mediators of the inflammatory response, stimulating the production and release of IL-6. IL-6 is a multifunctional cytokine influencing B-lymphocytes and T-lymphocytes, and it induces the production of acute-phase proteins in the liver, such as CRP, antiproteinases, and fibrinogen.[2] Furthermore IL-6 induces the proliferation of immature polymorphnuclear neutrophils (PNMs) in the circulation and stimulates mature PNMs to release superoxide anion (O_2^-).[13] IL-6 has been suggested as a marker of surgical stress, and it has been shown that the release of IL-6 correlates with the extent of tissue injury, duration of surgery, and volume of intraoperative blood loss.[13] In addition, liver resection itself induces the production of IL-6.[12] In liver surgery, the magnitude of the IL-6 release is enhanced by the use of pedicle clamping, due to the ischemia/reperfusion injury.[7–10] In contrast, IL-10 represents an anti-inflammatory cytokine, which downregulates the inflammatory response during the early postoperative period by modulating the activity of TNF-α, IL-6, IL1-α, and IL-1β activity.[5,14] However, nonphysiologic postoperative elevation of IL-10 may result in immunosuppression.[2] Therefore, the balance between pro- and anti-inflammatory cytokines is important for achieving an adequate immune response for surgical trauma, otherwise an exaggerated hyper- or hypoinflammatory response may result in an impaired host defense, with increased susceptibility to postoperative infectious and septic complications.[15] Overproduction of cytokines may also lead to the systemic inflammatory response syndrome (SIRS), with consecutive multiorgan dysfunction.[16]

To modulate the overproduction of proinflammatory cytokines, perioperative treatment with steroids has been demonstrated in cardiac, thoracic, and abdominal surgery.[17] In liver surgery, it has been shown that the preoperative administration of steroids reduces the cytokine release associated with ischemia-reperfusion injury when the pedicle clamping technique is used.[7–10] The effect of preoperative steroid administration in liver surgery without the Pringle maneuver has not been investigated until now. The effect of steroid administration is based on specific receptor-mediated and receptor-independent effects. Primarily, the suppression of postsurgical cytokine release from monocytes is caused by the inhibition of the messenger RNA.[18] Furthermore, steroids have lysosome membrane-stabilizing effects and protect the cells against lipid peroxidation.[19] Because steroids have no effect on cytokines that have already been released, it is important to reach a high dose during the early stage of the operation.[17] The optimal glucocorticoid preparation, timing of administration, and dosage remain a matter of debate (Table 3). We used MP because of the higher anti-inflammatory potency and reduced alteration of electrolyte and metabolic status relative to cortisol. A single shot of 30 mg/kg per body weight reduced the inflammatory response in several clinical and experimental studies.[17] However, a single dose of 500 mg was also sufficient to modify the early inflammatory response.[8,10] Because the onset of the anti-inflammatory effects of steroids is 1 to 2 h, glucocorticoid administration should be performed within this interval before surgery.[17]

Although the Pringle maneuver was not utilized in our series, the levels of the proinflammatory cytokines IL-6 and IL-8 were significantly lower in the steroid group than in the control group. However, compared to the reported high postoperative proinflammatory cytokine levels in studies in which the Pringle maneuver was used, the cytokine levels in our patients were much less exaggerated after surgery.[7–10] Subsequently, the acute-phase protein CRP, which is mainly induced by IL-6, was significantly suppressed in the steroid group in comparison to the control group. The moderate postoperative increase of IL-10 in the steroid group might be explained by the suppression of TNF-α. In addition to the suppression of the inflammatory response, it has been shown that steroid administration significantly lowered liver cell damage.[10] In our study, the postoperative ALT level and PT-INR were lower in the steroid group; however, the difference was not significant. This might reflect a protective role of the steroids against impaired coagulation balance and hepatocyte damage. On the other hand, the relatively low ALT levels in both groups can be explained by the renunciation of pedicle clamping in our series. The lower total bilirubin level in the steroid group might be the result of a faster recovery of the liver. Muratore et al.[9] observed modified transaminases and PT following steroid administration only in patients with chronic liver disease. In the study of Yamashita et al.,[8] the total bilirubin level was also significantly lower in the steroid group, whereas the transaminases were not suppressed. Further studies with more patients are necessary to investigate the influence of steroids on hepatic damage and liver function.

Although the preoperative administration of steroids seems to significantly reduce the inflammatory reaction, there are some concerns about negative effects on immune status, liver regeneration after resection, and wound healing. The present study shows that preoperative steroid administration does not affect the cellular immunity. In the steroid group, the LPS-induced TNF-α release was only temporarily reduced immediately after surgery, followed by a fast increase. However, only prolonged monocyte deactivation for several days enhances the susceptibility to infection.[20] Additionally, we found no differences in the postoperative expression of HLA-DR on monocytes between the two groups. Reduced

Table 3. Human studies of steroid administration during partial hepatectomy

Author	Year	*n*	Dosage/Timing	Hepatic damage	Inflammatory response
Shimada et al.[7]	1996	17	30 mg/kg BW 3 h before surgery	AST ↔	IL-6 ↓ CRP ↓
Yamashita et al.[8]	2001	33	500 mg 2 h before surgery	AST, ALT ↔	IL-6 ↓ IL-10 ↑
Muratore et al.[9]	2003	53	30 mg/kg per BW 30 min before surgery	Normal liver: AST, ALT, ↔ cholestatic liver: ↓	IL-6 ↓
Aldrighetti et al.[10]	2006	76	500 mg before induction of anesthesia	AST, ALT ↓	IL-6, TNF-α ↓
Schmidt et al. (present study)	2006	20	30 mg/kg per BW 90 min before surgery	ALT ↔	IL-6 ↓ IL-8 ↓ IL-10 ↔ CRP ↓ HLA-DR ↔

expression of HLA-DR was shown to be associated with an increased risk of infection and a significant short-term outcome after major surgery.[21] Furthermore, Yamashita et al.[8] previously reported that preoperative administration of steroids suppressed the serum values of immunosuppressive antigen and the positive rate of serum candida antigen, a marker of bacterial translocation. They concluded that preoperative administration of steroids preserved the postoperative immune function. This is of great clinical interest, not only because of the decreased susceptibility to septic complications, but also in oncologic surgery, because a better-preserved postoperative immune system may inhibit tumor cells from establishing metastases.[22] Another major concern about the administration of preoperative steroids in liver surgery was the potential negative effect on the regeneration of the remnant liver after resection, due to the suppression of inflammatory cytokines, especially IL-6, which play a key role in liver regeneration.[23] While IL-6 promotes cell-cycle progression after hepatectomy, it has been demonstrated that the overproduction of IL-6 may inhibit liver regeneration.[24] In accordance with Yamashita et al.,[8] Muratore et al.,[9] and Aldrighetti et al.,[10] we found no negative effects of the steroid in regard to hepatocyte damage or recovery of the remnant liver (ALT, bilirubin, PT-INR). Comparing the resected liver in a rat model with and without preoperative high-dose steroid administration, Glanemann et al.[25] showed that the steroid administration did not influence postoperative liver regeneration.

In this study we did not notice an advantage of steroid administration on the postoperative complication rate or convalescence. The significantly shorter hospital stay in the steroid group can be explained by the prolonged hospital stay of the patient in the control group who developed biliary stenosis and a wound abscess. While Yamashita et al.[8] and Muratore et al.[9] found no improvement in the postoperative clinical course in patients undergoing liver surgery with preoperative steroids, a recently published prospective study has demonstrated reduced postoperative complications and earlier discharge of the patients in the steroid group.[10] Especially in high-risk patients with impaired cardiopulmonary function, preoperative steroid administration may contribute toward achieving a better postoperative course due to the membrane-stabilizing effects on vascular endothelial cell membranes, the suppression of local edema, and the improvement of the microcirculation that results in the reduction of tissue trauma.[6,26–28] In liver surgery, Kimura et al.[29] demonstrated a hyperactive proinflammatory cytokine response and a high incidence of postoperative infection in patients with preoperative biliary obstruction compared to those without. The evaluation of preoperative steroid treatment is necessary in these high-risk patients.

In conclusion, this prospective randomized trial has demonstrated a significant suppression of the surgical stress response in liver surgery without pedicle clamping after preoperative pulse therapy with high-dose MP, without affecting the cellular immunity. To elucidate the impact of a preoperative steroid bolus on the short-term clinical course, further studies with more patients are needed.

References

1. Faist E, Schinkel C, Zimmer S. Update on the mechanisms of immune suppression of injury and immune modulation. World J Surg 1996;20:454–9.
2. Menger MD, Vollmar B. Surgical trauma: hyperinflammation versus immunosuppression? Langenbecks Arch Surg 2004;389: 475–84.
3. Lin E, Calvano SE, Lowry SF. Inflammatory cytokines and cell response in surgery. Surgery 2000;127:117–26.
4. Members of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864–74.
5. Jerin A, Pozar-Lukanovic N, Sojar V, Stanisavljevic D, Paver-Erzen V, Osredkar J. Balance of pro- and anti-inflammatory cytokines in liver surgery. Clin Chem Lab Med 2003;41:899–903.
6. Nagelschmidt M, Fu ZX, Saad S, Dimmeler S, Neugebauer E. Preoperative high dose methylprednisolone improves patients outcome after abdominal surgery. Eur J Surg 1999;165:971–8.
7. Shimada M, Saitoh A, Kano T, Takenaka K, Sugimachi K. The effect of a perioperative steroid pulse on surgical stress in hepatic resection. Int Surg 1996;81:49–51.
8. Yamashita Y, Shimada M, Hamatsu T, Rikimaru T, Tanaka S, Shirabe K, Sugimachi K. Effects of preoperative steroid administration on surgical stress in hepatic resection: prospective randomized trial. Arch Surg 2001;136:328–33.
9. Muratore A, Ribero D, Ferrero A, Bergero R, Capussotti L. Prospective randomized study of steroids in the prevention of ischaemic injury during hepatic resection with pedicle clamping. Br J Surg 2003;90:17–22.
10. Aldrighetti L, Pulitano C, Arru M, Finazzi R, Catena M, Soldini L, et al. Impact of preoperative steroids administration on ischemia-reperfusion injury and systemic responses in liver surgery: a prospective randomized study. Liver Transpl 2006;12:941–9.
11. Docke WD, Hoflich C, Davis KA, Rottgers K, Meisel C, Kiefer P, et al. Monitoring temporary immunodepression by flow cytometric measurement of monocytic HLA-DR expression: a multicenter standardized study. Clin Chem 2005;51:2341–7.
12. Kimura F, Shimizu H, Yoshidome H, Ohtsuka M, Kato A, Yoshitomi H, et al. Circulating cytokines, chemokines, and stress hormones are increased in patients with organ dysfunction following liver resection. J Surg Res 2006;133:102–12.
13. Biffl WL, Moore EE, Moore FA, Peterson VM. Interleukin-6 in the injured patient. Marker of injury or mediator of inflammation? Ann Surg 1996;224:647–64.
14. Pradier O, Willems F, Abramowicz D, Schandene L, de Boer M, Thielemans K, et al. CD40 engagement induces monocyte procoagulant activity through an interleukin-10 resistant pathway. Eur J Immunol 1996;26:3048–54.
15. Hensler T, Hecker H, Heeg K, Heidecke CD, Bartels H, Barthlen W, et al. Distinct mechanisms of immunosuppression as a consequence of major surgery. Infect Immun 1997;65:2283–91.
16. Nystrom PO. The systemic inflammatory response syndrome: definitions and aetiology. J Antimicrob Chemother 1998;41 (Suppl A):1–7.

17. Holte K, Kehlet H. Perioperative single-dose glucocorticoid administration: pathophysiologic effects and clinical implications. J Am Coll Surg 2002;195:694–712.
18. Scheinman RI, Gualberto A, Jewell CM, Cidlowski JA, Baldwin AS Jr. Characterization of mechanisms involved in transrepression of NF-kappa B by activated glucocorticoid receptors. Mol Cell Biol 1995;15:943–53.
19. Braughler JM. Lipid peroxidation-induced inhibition of gamma-aminobutyric acid uptake in rat brain synaptosomes. J Neurochem 1985;44:1282–8.
20. Volk HD, Thieme M, Heym S, Docke WD, Ruppe U, Tausch W, et al. Alterations in function and phenotype of monocytes from patients with septic disease—predictive value and new therapeutic strategies. Behring Inst Mitt 1991;88:208–15.
21. Buunen M, Gholghesaei M, Veldkamp R, Meijer DW, Bonjer HJ, Bouvy ND. Stress response to laparoscopic surgery: a review. Surg Endosc 2004;18:1022–8.
22. Carter JJ, Whelan RL. The immunologic consequences of laparoscopy in oncology. Surg Oncol Clin N Am 2001;10:655–77.
23. Streetz KL, Luedde T, Manns MP, Trautwein C. Interleukin 6 and liver regeneration. Gut 2000;47:309–12.
24. Wustefeld T, Rakemann T, Kubicka S, Manns MP, Trautwein C. Hyperstimulation with interleukin 6 inhibits cell cycle progression after hepatectomy in mice. Hepatology 2000;32:514–22.
25. Glanemann M, Munchow S, Schirmeier A, Al-Abadi H, Lippek F, Langrehr JM, et al. Steroid administration before partial hepatectomy with temporary inflow occlusion does not influence cyclin D1 and Ki-67 related liver regeneration. Langenbecks Arch Surg 2004;389:380–6.
26. Sauerland S, Nagelschmidt M, Mallmann P, Neugebauer EAM. Risk and benefits of preoperative high dose methylprednisolone in surgical patients. A systematic review. Drug Saf 2000;23:449–61.
27. Takeda S, Ogawa R, Nakanishi K, Kim C, Miyashita M, Sasajima K, et al. The effect of preoperative high dose methylprednisolone in attenuating the metabolic response after oesophageal resection. Eur J Surg 1997;163:511–7.
28. Sato N, Koeda K, Ikeda K, Kimura Y, Aoki K, Iwaya T, et al. 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 2002;236:184–90.
29. Kimura F, Miyazaki M, Suwa T, Itoh H, Ambiru S, Shimizu H, Nakagawa K. Hyperactive cytokine response after partial hepatectomy in patients with biliary obstruction. Eur Surg Res 1998;30:259–67.