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Risks and Benefits of Preoperative High Dose Methylprednisolone in Surgical Patients

A Systematic Review

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Abstract

Background: A single preoperative high dose of methylprednisolone (15 to 30 mg/kg) has been advocated in surgery, because it may inhibit the surgical stress response and thereby improve postoperative outcome and convalescence. However, these potential clinical benefits must be weighed against possible adverse effects.

Objective: To conduct a risk-benefit analysis using a meta-analysis, to compare complication rates and clinical advantages associated with the use of high dose methylprednisolone in surgical patients.

Methods: Randomised controlled trials of high dose methylprednisolone in elective and trauma surgery were systematically searched for in various literature databases. Outcome data on adverse effects, postoperative pain and hospital stay were extracted and statistically pooled in fixed-effects meta-analyses.

Results: We located 51 studies in elective cardiac and noncardiac surgery, as well as traumatology. Pooled data failed to show any significant increase in complication rates. In patients treated with corticosteroids, nonsignificantly more gastrointestinal bleeding and wound complications were observed; the 95% confidence interval boundaries of the numbers-needed-to-harm were 59 and 38, respectively. The only significant finding was a reduction of pulmonary complications (risk difference –3.5%; 95% confidence interval –1.0 to –6.1), mainly in trauma patients.

Conclusion: For patients undergoing surgical procedures, a perioperative single-shot administration of high dose methylprednisolone is not associated with a significant increase in the incidence of adverse effects. In patients with multiple fractures, limited evidence suggests promising benefits of glucocorticoids on pulmonary complications.

Glucocorticoids have many important physiological effects, which explains their therapeutic use in a wide variety of clinical situations. Today, about 0.5% of the general population continuously take a corticosteroid medication,[1] although corticosteroids have many well recognised adverse effects, most of which are dependent on dosage and duration of therapy.[2-5] Those, however, who generalise from glucocorticoid adverse effects during continuous administration, probably exaggerate the adverse effect rate during short term and single-shot administration ('steroid-phobia').[6,7]

While treatment with low, medium and high dose corticosteroids is routine in many diseases, glucocorticoids are currently being studied in surgery in an even higher dosage: by administering a single or repeated intravenous high dose of methylprednisolone sodium succinate (MPSS) researchers try to block the pathways by which immunoactivation causes cellular damage and undesired clinical outcomes.[8,9] A dose of 15 to 30 mg/kg is necessary to reach these nongenomic, membrane-stabilising effects.[10-13] While corticosteroids (given as a high dose bolus and followed by an infusion for 1 day) are already established as effective in spinal cord injury,[14-16] they have been shown to be of little or even no benefit in traumatic brain injury.[17] Furthermore, cardiac surgeons have been using high dose MPSS since 1975 in patients undergoing coronary artery bypass to mitigate the consequences of ischaemia-reperfusion-injury.[18] Within the same decade, Scandinavian surgeons began to use MPSS in patients with multiple injuries,[19,20] and in thoracic,[21] abdominal[22] and joint surgery.[23]

The pathophysiological background of this treatment has been extensively studied both in animals and humans. Many immunological and inflammatory markers have been found to be suppressed by glucocorticoid pretreatment, such as nitric oxide, adhesion molecules,[8] granulocyte adhesion,[24] interferon-γ, interleukin-1β, 2, 3, 5, 6, and 8, tumour necrosis factor,[25] as well as bradykinin, histamine, serotonin and eicosanoids.[26] Because glucocorticoid suppression protects the organism from the mediator response to surgical trauma, it presumably also may lead to less pain and fatigue,[27] and finally a shorter hospital stay and quicker recovery time for the patient.[28]

We wanted to compare these possible benefits against the adverse effects of high dose MPSS in elective surgery and trauma patients, who pre- or perioperatively received a single infusion or short term course (≤3 days) of MPSS. We therefore performed a systematic review of the literature with subsequent meta-analysis to assess the net benefit of glucocorticoid treatment.[29,30]

Methods

Study Inclusion Criteria

All randomised controlled trials that compared high dose MPSS with placebo or no treatment in patients undergoing surgery were considered as potentially relevant. As 'high dose', we defined any intravenous dose exceeding 15 mg/kg or 1g MPSS given as a single or repeated dose within a maximum of 3 days and discontinued afterwards. We did not include studies that recruited patients who routinely required intensive care at study entry, because the incidence of adverse effects may be much higher in these patients. Similarly, we excluded trials, that concerned only a very small operative intervention, which usually is performed on an outpatient basis (mainly oral and facial surgery). Thus, in all included studies patients have a comparable medium severity of injury and immunoactivation, caused either by surgery or by trauma.

For the analysis of potential adverse effects we concentrated on the most important ones. We used the outcome definitions of the primary studies to define: (i) significant gastrointestinal bleeding; (ii) infection, bleeding, leakage, or seroma of a wound; (iii) pulmonary complications, for example pneumonia, fat embolism syndrome, adult respiratory distress syndrome, or any other respiratory failure; (iv) psychiatric complications, for example psychotic or affective disorders. (v) symptomatic avascular bone necrosis proven by x-ray and; (vi) death from any cause. Hyperglycaemia and hypotension were not included, because these clinical

events are of varying severity and relevance, and are described only inadequately in the primary trials.

Only the trials on preoperative MPSS administration in elective noncardiac surgery were used to assess the benefits of this treatment regimen in these patients. Here we extracted the data on postoperative pain at rest, fatigue,[31] mobilisation, and hospital stay. Patient-relevant outcome data for cardiac and trauma surgery patients were not analysed, since the clinical course in these patients is determined by very different factors than in other types of surgery. (Clinical data are also not recorded in most of these cardiac and trauma surgery papers, as it later turned out.)

Literature Search and Statistical Analysis

Our primary tool for the literature search was the internet-based Medline-database 'Pubmed'. To search for relevant articles we combined the medical subject heading 'methylprednisolone' with the publication type 'randomised controlled trial'. A similar search was performed in the Cochrane Library (Version II/2000). Both searches were most recently repeated in August, 2000. The references of all articles and 2 related Cochrane reviews were checked for further studies.[16,17] Additionally we contacted Hoechst Marion Roussel Germany Inc., the producer of a commonly used MPSS (Urbason®), and asked for further information on relevant trials.

Study selection, data extraction, and data entry were performed by a single observer. When there was doubt whether a paper should be included, the decision was made by a second investigator who was unaware of the study results. We grouped the articles into 3 categories (table I). Category A studies were studies that reported complication rates and patient-relevant outcome measures, such as hospital stay or pain. Category B studies consisted of trials that described clinical complications or stated that no such complications had been observed. If only 1 type of complication was described but other types were not specifically mentioned, the paper was included on the assumption that no other complications had occurred. Category C studies consisted of clinical trials which assessed pathophysiology or immunology. For these trials, that did not

Table I. Distribution of all 51 trials according to surgical field and quality of reporting

Category	Elective noncardiac surgery	Elective cardiac surgery	Trauma surgery	Spinal cord injury
Category A: trials which report clinical outcomes	Bigler et al.[32]; Komori et al.[33]; Launo et al.[34]; Nagelschmidt et al.[35]; Schulze et al.[36]; Sumida et al.[37]; Takeda et al.[38]; Tønneson et al.[21]; Zotti et al.[39]	Chaney et al.[40,41]; Engelman et al.[42]; Fecht et al.[43]; Niazi et al.[44]; Tassani et al.[45]		Bracken et al.[14,15]; Otani et al.[46,47]; Petitjean[48,49]; Pettersson et al.[50]
Category B: trials which report side effects	Høgevold et al.[51,52]; Gammer et al.[53]	Andersen et al.[54]; Jansen et al.[55]; Mayumi et al.[56]; Morton et al.[57]; Toft et al.[58]; Toledo-Pereyra[59]; Rao et al.[60]; Wan et al.[61,62]	Alho et al.[63,64]; Lindeque et al.[65]; Rokkanen et al.[19]; Schonfeld et al.[66]; Stoltenberg et al.[67]; Svennevig[20,68-70]	
Catagory C: trials where neither clinical outcomes nor adverse effects are reported	Mikawa et al.[71]; Edfeldt and Thomson[72]	Boscoe et al.[73]; Diego et al.[74]; Enderby et al.[75]; Ferries et al.[76]; Fosse et al.[77]; Hill et al.[78,79]; Jorens et al.[80]; Karlstad et al.[81]; Kawamura et al.[82,83]; Kobayashi[84]; Loubser et al[85,86]; Tabardel[87]; Thompson et al. #1[88]; Thompson et al. #2[89]		

state the (non) occurrence of complications, we only assumed that no mortality occurred, since a fatality would have resulted in missing data in the analysis of variables.

As a measure of effect we chose the risk difference for dichotomous variables and the weighted mean difference for continuous variables. The risk difference has been shown to be conservative in the analysis of rare events.[90] In 1 study, data on hospital stay were reported as medians and ranges. Here, we estimated the differences of means and medians between treatment and control groups to be equivalent; standard deviations were approximated as being half the reported range. This approach tends to be cautious, as it assigns a lower statistical weighting factor to such incompletely reported studies. No efforts were made to contact authors.

For statistical analysis we used the Cochrane Collaboration's software RevMan 4.0.4 with MetaView 3.1. In case there was no statistical evidence of heterogeneity among the primary studies (as defined by $p < 0.1$ in the χ^2-test), we employed a fixed effects model. To enable easy interpretation of the results we used 95% confidence intervals (CIs) and calculated the number-needed-to-harm (NNH). The NNH specifies how many patients have to be treated on average before an adverse effect is noted.[91] The NNH is calculated as the inverse of the risk difference, but can also be derived from an odds ratio or relative risk. We used the lower 95% CI bound-

Table II. Randomised controlled trials investigating the effect of high dose methylprednisolone sodium succinate in elective noncardiac surgery patients (in alphabetical order)

Reference (year)	Type of operation	No. of patients	Route of administration and dose	Outcomes reported (besides complications)
Bigler et al.[32] (1996)	Lung surgery (lobectomy or pneumectomy)	36	IV 25 mg/kg	Pain, lung function (FEV_1), hospital stay
Edfeldt and Thomson[72] (1980)	Knee replacement for knee osteoarthritis	26	IV 30 mg/kg	Lung function (PaO_2), haemodynamic parameters
Gammer et al.[53] (1998)	Hip replacement for hip osteoarthritis	30	IV 2g	Lung function (PaO_2), complement activation (C3a, C5a)
Høgevold et al.[51,52] (1991)	Hip replacement for hip osteoarthritis	12	IV 3 doses of 30 mg/kg each	Immunological markers, laboratory parameters
Komori et al.[33] (1999)	Elective abdominal aortic aneurysm repair	20	IV 1g	Immunological markers, laboratory parameters, hospital stay
Launo et al.[34] (1990)	Lung surgery (lobectomy or pneumectomy)	40	IV 30 mg/kg	Pain, laboratory parameters, circulatory parameters
Mikawa et al.[71] (1990)	Lung surgery (lobectomy)	28	IV 30 mg/kg	Laboratory parameters
Nagelschmidt et al.[35] (1999)	Abdominal surgery/ incisional hernia repair	20	IV 30 mg/kg	Fatigue, pain, analgesics consumption, mobilisation, lung function (FEV_1), hospital stay
Schulze et al.[36] (1997)	Colonic resection	24	IV 30 mg/kg	Fatigue, pain, analgesics consumption, mobilsation, lung function (FEV_1), hospital stay
Sumida et al.[37] (1999)	Gastric resection and intraperitoneal hyperthermia	20	IV 2 doses of 25 mg/kg each	Immunological and haemodynamic parameters, lung injury score
Takeda et al.[38] (1997)	Oesophageal resection	30	IV 30 mg/kg	Lung function (PaO_2 : FiO2-ratio), ICU stay, hospital stay
Tønneson et al.[21] (1993)	Lung surgery (lobectomy, pneumectomy or subsegmental resection)	21	IV 30 mg/kg	Immunological markers, hospital stay
Zotti et al.[39] (1988)	Abdominal surgery (vascular, pancreatic or hepatic)	82	IV 30 mg/kg	Lung function (PaO_2, $PaCO_2$ HO_3)

FiO_2 = inspired oxygen fraction; **FEV_1** = forced expiratory volume in 1s; **ICU** = intensive care unit; **IV** = intravenous; **$PaCO_2$** = partial carbon dioxide pressure; **PaO_2** = partial oxygen pressure.

Table III. Randomised controlled trials investigating the effect of high dose methylprednisolone sodium succinate in trauma patients.

Reference (year)	Type of trauma	No. of patients	Route of administration and dose	Outcome
Alho[63] (1978)	At least 2 fractures in the pelvis, femur or tibia. No severe cerebral, thoracic or abdominal injuries	60	IV 3 doses of 10 mg/kg each. At admission, at 8 and 16 hours post trauma	Incidence of fat embolism syndrome
Rokkanen et al.[19] (1974)	At least 1 critical or 3 moderate injuries	29	IV 3 doses of 10 mg/kg each. At admission, at 8 and 16 hours post trauma	Incidence of fat embolism syndrome
Schonfeld et al.[66] (1983)	1 or more lower-extremity, long-bone fractures. No major cerebral, thoracic or abdominal injuries	64	IV 7.5 mg/kg every 6 hours for 12 doses, for a total of 90 mg/kg	Incidence of fat embolism syndrome, physiological and laboratory parameters
Stoltenberg and Gustilo[67] (1979)	Femoral or tibial fracture	43	IV 2 doses of 1g	Incidence of fat embolism syndrome, lung function (PaO_2)
Svennevig et al.[68,69] (1984)	Blunt chest injury (a minimum of 4 broken ribs)	40	IV 30 mg/kg	Incidence of fat embolism syndrome, haemodynamic parameters
Lindeque et al.[65] (1987)	Femoral and/or tibial fracture. No major cerebral, thoracic or abdominal injuries.	55	IV 2 doses of 30 mg/kg	Incidence of fat embolism syndrome, lung function (PaO_2), complement activation (C5a), free fatty acids

IV = intravenous; **$Pa0_2$** = partial oxygen pressure.

ary of the NNH to describe the largest increase in the adverse effect rate that could be ruled out by our analysis. The number-needed-to-treat is the NNH's counterpart for describing beneficial effects. It is calculated the same way as the NNH.

Results

Literature Search

Out of 9065 articles on 'methylprednisolone' we identified 693 randomised controlled trials, of which 95 were reviewed in detail to judge their eligibility. We excluded pseudo- or nonrandomised trials,[92-95] trials on less invasive interventions (such as coronary stenting,[96,97] facial[98] or oral surgery[99]), paediatric trials,[100,101] trials of medium or low dose MPSS,[82,102-107] dexamethasone,[108-110] or more than 1 intervention.[111] All trials involving head injury used either medium doses or extended therapy over more than 3 days, and therefore were excluded.

In summary, 51 studies met our selection criteria (table I). Multiple reports of the same patient population were combined. Most publications were written in English, but 2 were written in Japanese, 1 in Italian, 1 in French and 1 in Spanish. The included studies were performed in: elective cardiac surgery (28 trials),[41-45,54-62,73-89,112] elective noncardiac surgery (13 trials) [table II],[21,23,32-39,51-53,71,72] trauma surgery (6 trials) [table III],[19,20,63-70] and spine surgery (4 trials).[14,15,46-50] Most studies involved only very small numbers of patients, and half of the trials in cardiac surgery did not report any clinical result.[73-89] The methodologic quality of the 51 trials was poor, since 26 trials (51%) were not placebo-controlled and 32 (63%) did not describe their technique of randomisation and the concealment of allocation.

Benefits of Methylprednisolone Sodium Succinate (MPSS)

In the 13 trials where MPSS was administered preoperatively to patients undergoing elective surgery, quite different surgical procedures have been examined (table II). Four studies reported pain levels on day 1 after surgery, but different methods of pain measurement and reporting precluded meta-analysis: Launo et al.[34] stated that only 65% of pa-

Table IV. Main results for beneficial and adverse effects of high dose methylprednisolone sodium succinate as compared with placebo or no corticosteroid

Outcome variable	Studies (n)	Events (n_1/n_2)	Patients (N_1/N_2)	Pooled results (95% CI)	Number needed to harm/treat (95% CI)
Pain (day 1)	4	a	a	a	a
Fatigue (day 1)	2	b	b	b	b
Mobilisation	2	b	b	b	b
Hospital stay	4	NA	45/46	–1.0 days (–3.2 to +1.2)	NA
Gastrointestinal bleeding	34	10/7	973/1003	RD +0.3% (–1.0 to +1.7)	NNH: 333 (lower CI 59)
Wound complications	34	28/20	972/997	RD +1.0% (–7 to +2.6)	NNH: 100 (lower CI 38)
Pulmonary complications	35	74/115	981/1011	RD –3.5% (–6.1 to –1.0)	NNT: 29 (16 to 100)
Psychiatric complications	35	c	c	c	c
Avascular bone	35	c	d	c	c
Death of any case	50[d]	20/32	1170/1190	RD –0.9% (–2.5 to +0.6)	NNT: 111

a Data did not allow meta-analysis.

b Too little data available.

c No events in either group.

d Morton et al.[57] state that 1 of their patients died, but it is left unclear whether this patient received MPSS or placebo.

95% CI = 95% confidence intervals; **NA** = not applicable; **NNH** = number needed to harm; **NNT** = number needed to treat; **RD** = risk difference.

tients treated with MPSS complained of pain as compared to 90% in the control group. Bigler[32] measured pain on a 0 to 4 scale (with 0 indicating no pain) and found significantly less pain on day 1 in the MPSS group (median pain intensity in control *vs* therapy group was light *vs* absent). Schulze et al.[36] measured pain with the visual analogue scale; most of the patients treated with MPSS in this study were free of pain, while the control group experienced median pain levels of 13 (not significant). Nagelschmidt et al.[35] and Fu et al.[113] described a reduction of pain levels by 45% (mean 36,1 *vs* 19,8; SD 23 *vs* 20 for control and MPSS group, p = not significant); they also found a reduced consumption of analgesics in the MPSS group.

Fatigue and reconvalescence were assessed only in 2 studies, which both yielded better results in the corticosteroid groups. However, in contrast to Nagelschmidt et al.,[35] who found large and significant benefits, Schulze et al.[36] noted somewhat smaller benefits, with only the mobilisation score being significantly improved.

Hospital stay was documented in 4 studies. While Takeda et al.[38] and Nagelschmidt et al.[35] noted a reduction in the length of hospital stay (37 *vs* 54 and 8.5 *vs* 13 days for MPSS and control group, respectively), Tønneson et al.[21] found a modest increase, and Komori et al.[33] saw no difference (14 *vs* 12 and 16.6 *vs* 17 days, respectively). *In summary*, a reduction of –1.9 days (95% CI –6.1 to +2.4) can be expected after MPSS administration.

Adverse Effects of MPSS

Relevant gastrointestinal bleeding was observed in 17 of the 1696 patients (table IV), resulting in an overall risk difference of +0.3% (95 CI –1.0 to +1.7). 14 of the 17 complications occurred in patients with spine injury, while none were noted in the elective noncardiac surgery trials. The lower boundary of 95% CI of the NNH is 59, thus indicating that on average we can rule out 1 additional gastrointestinal bleeding in less than 59 patients.

Wound complications were more common in elective noncardiac and spine surgery as compared with other fields. The overall risk difference of +1.0% (95% CI: –0.7 to +2.6) indicates a modest increase, although the 95% CI lower boundary of the NNH still is 38.

Pulmonary complications were noted in many of the trials. In the neurotrauma trials MPSS seemed to have little effect on lung function, but in the other groups MPSS had a strong protective effect with a significant reduction of pulmonary complications (fig. 1). This was most pronounced in the studies

that included patients with skeletal injury, where fat embolism syndrome had a high incidence. In this group the results also are strikingly homogeneous, while the overall analysis is hampered by nonsignificant heterogeneity among the 4 categories of studies.

Psychiatric adverse effects and avascular bone necrosis were not described in any of the 51 studies. The overall mortality rate was about equally distributed between patients treated with MPSS and patients given placebo.

Discussion

This study aimed at comparing the potential benefits and harms of high dose MPSS in patients, who undergo elective surgical procedures of medium severity (defined as routinely requiring postoperative hospital stay). *In summary*, the few available studies which assessed patient-relevant outcome criteria found similar benefits in regard to pain, fatigue and mobility. Regarding the adverse effects of MPSS we included a much broader group of primary trials. These trials – as well as our meta-analysis – did not find any significant increase in the incidence of severe complications after the infusion of high doses of MPSS. Pulmonary complications, on the other hand, were even significantly diminished, especially in trauma patients.

A critical aspect of our analysis is the assumption that a paper which reported a single complication, would also have reported other complications, if such complications occurred. However, this is an often made and reasonable assumption,[3,4] and we excluded those articles where complications were not mentioned at all. Critics may also find it arbitrary to combine study results from heterogeneous patient cohorts, such as cardiac surgery and hip replacement. However, we used the complication data (but not the clinical data) from these studies, because we think that surgical procedures of comparable severity also carry a comparable risk of general complications, such as gastrointestinal bleeding. We therefore excluded trials where the intervention was judged to be associated with only a minor degree of immunoactivation (such as transluminal coronary angioplasty or oral surgery). It may be noteworthy that also in these larger studies no major complications were noted,[96-99] as was the case in the phase I studies in healthy volunteers.[114,115] This renders future complications quite unlikely.[116]

Unfortunately, many of the included studies had their focus on pathophysiological or immunological parameters, which is problematic, as these surrogate parameters are not necessarily associated with the clinical outcome. Therefore, we refrained from aggregating such data, although data quite consistently showed that MPSS pretreatment lowers the postoperative levels of immunological parameters, e.g. cytokines, prostaglandins or nitric oxide. It also improved lung function in most of the studies that measured respiratory parameters. On the background of these findings the reduction in pulmonary complications that we observed can be easily accounted for. MPSS may therefore have benefits especially in patients at risk of pulmonary complications.

Since the 1950s, many articles have speculated on the association between corticosteroid therapy and gastrointestinal bleeding. Conn et al.[5,117] have repeatedly argued that this association is nothing more than a 'myth', while other meta-analysts noted a significant dose-dependent increase.[4] When extrapolating from 2 similar meta-analyses,[5,118] the dose-response relationship indicates that short term courses of glucocorticoids (<2 days) do not carry an increased risk of gastrointestinal bleeding. We excluded studies that used medium dosages or extended courses, although this would have enabled us to evaluate a possible dose-response relationship.[119] However, there are only a few studies available that looked at regimens other than high dose regimens in surgical patients.

We are aware of the fact that some nonrandomised studies have described serious complications after glucocorticoid administration, such as pneumonia.[120-122] However, these findings can mainly be explained by the selection of more severely ill patients into an MPSS treatment regimen. It is well known that nonrandomised studies often give completely different results than randomised ones and

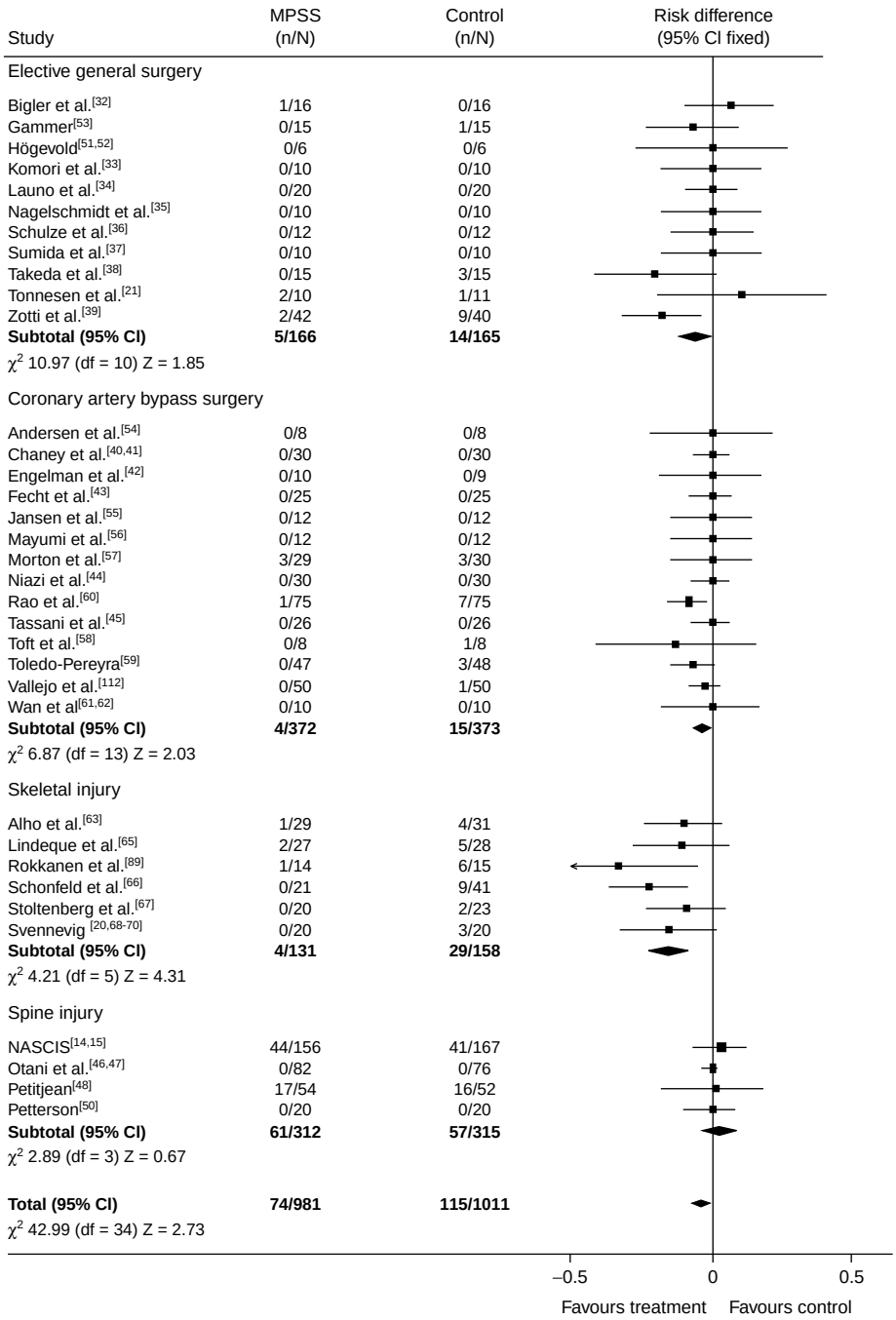

Fig. 1 Rates of pulmonary complications after methylprednisolone sodium succinate (MPSS) or placebo (control). Trial results are grouped according to patient characteristics. Result bars [representing 95% confidence intervals (CI)] that lie left of the verticle line indicate a protective effect of corticosteroids. Z-scores exceed 1.96, if pooled results are significant. The overall result shows a risk difference of -3.2% (95% CI -6.3 to -0.3), but mild heterogeneity is present ($p = 0.1573$; α^2-statistics).

that such studies should be interpreted carefully.[123] Just as little information is added by case reports, although serious or even lethal adverse effects have been described.[124-131] Most of these reports involve patients with serious comorbidity (mainly cardiovascular). The patients considered in this meta-analysis are only partly representative of this general patient population, since the eligibility criteria of many clinical trials exclude patients with comorbidity, concomitant drug therapy, or other risk factors. Thus, clinicians should carefully take into account such individual risk factors, before considering our results generalisable to the patient at hand.

Randomised trials are regarded as the most credible way of comparing medical treatments. Still, it has to be recognised that the quality of most randomised trials included in this meta-analysis is poor, thus making interpretation of these trials difficult. Poor allocation concealment (which was the case in probably half of the present trials) has been shown to be associated with exaggerated treatment effects.[132] However, the fact that most of the trials failed to report their randomisation procedure does not necessarily imply that these methods were inadequate. With regard to the nonblinded design of many primary trials, it can be speculated that adverse effects are more likely to be detected in corticosteroid-treated than in control patients, since physicians may expect a higher incidence of adverse effects. This effect, called expectation bias, could lead to an overestimation of the true adverse effect rates.

To date, only very few data are available on the advantages of MPSS in patients undergoing elective surgery. The results of the admittedly very small and heterogeneous studies are promising, but we have to bear in mind that the reduction of pain levels may still be caused by the euphoric effect of MPSS rather than by an attenuation of the immunosystem.[133] Although we found no evidence of any severe psychiatric adverse effect, the less pronounced effects of MPSS on mood should be kept in mind.[134] However, if pain is seen in conjunction with other parameters, it seems unlikely that pain reduction is fully explainable by the central nervous effects of MPSS.

Avascular necrosis of bone is an important complication during corticosteroid therapy. Again, not a single case was reported within the primary studies of our review. It may be argued that the follow-up period in many of these trials was too short to detect such an event, but Felson and Anderson[135] also found corticosteroid bolus dose unassociated with bone necrosis risk. In their analysis they had compared different dosages and regimens of corticosteroids across several studies coming from different fields.

Conclusion

This meta-analysis, based on the data from nearly 2500 patients, failed to find any significant increase in adverse effect rates after a short term or single dose administration of high dose MPSS. Some trials even described beneficial effects of MPSS, for instance a reduction of pulmonary complications in trauma patients. The studies that now are necessary to fully prove these benefits can be performed on the evidence-base that a single dose (or short term) administration of high dose MPSS is not associated with a significant increase in the incidence of adverse effects.

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References

1. Walsh LJ, Wong CA, Pringle M, et al. Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross sectional study. BMJ 1996; 313: 344-6
2. Boston Collaborative Drug Surveillance Program. Acute adverse reactions to prednisone in relation to dosage. Clin Pharmacol 1972; 13: 694-8
3. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. Rev Infect Dis 1989; 11: 954-63

4. Messer J, Reitman D, Sacks HS, et al. Association of adrenocorticosteroid therapy and peptic-ulcer disease. N Engl J Med 1983; 309: 21-4
5. Conn HO, Poynard T. Corticosteroids and peptic ulcer: meta-analysis of adverse events during steroid therapy. J Intern Med 1994; 236: 619-32
6. Robbins JJ. Steroid side effects, a credibility gap between fact and opinion [letter]. N Engl J Med 1968; 279: 328
7. Tuft L. "Steroid-phobia" in asthma management. Ann Allergy 1979; 42: 152-9
8. Cronstein BN, Kimmel SC, Levin RI, et al. A mechanism for the antiinflammatory effects of corticosteroids: the glucocorticoid receptor regulates leukocyte adhesion to endothelial cells and expression of endothelial-leukocyte adhesion molecule 1 and intercellular adhesion molecule 1. Proc Natl Acad Sci U S A 1992; 89: 9991-5
9. Weiler JM, Packard BD. Methylprednisolone inhibits the alternative and amplification pathways of complement. Infect Immun 1982; 38: 122-6
10. Buttgereit F, Dimmeler S, Neugebauer E, et al. Mechanisms of action of high-dosage glucocorticoid therapy [in German]. Dtsch Med Wochenschr 1996; 121: 248-52
11. Hall ED. The neuroprotective pharmacology of methylprednisolone. J Neurosurg 1992; 76: 13-22
12. Munck A, Naray-Fejes-Toth A. Glucocorticoids and stress: permissive and suppressive actions. Ann N Y Acad Sci 1994; 746: 115-30
13. Lipworth BJ. Therapeutic implications of non-genomic glucocorticoid activity. Lancet 2000; 356: 87-9
14. Bracken MB, Shepard MJ, Collins WF, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. N Engl J Med 1990; 322: 1405-11
15. Bracken MB, Shepard MJ, Collins WF, Jr., et al. Methylprednisolone or naloxone treatment after acute spinal cord injury: 1-year follow-up data. Results of the second National Acute Spinal Cord Injury Study. J Neurosurg 1992; 76: 23-31
16. Bracken MB. Pharmacological interventions for acute spinal cord injury [Cochrane Review]. In: Cochrane Collaboration, editor. The Cochrane Library, Issue 1/2000 [CD-ROM]. Oxford/UK: Update Software, 2000
17. Alderson P, Roberts I. Corticosteroids in acute traumatic brain injury [Cochrane Review]. In: Cochrane Collaboration, editor. The Cochrane Library, Issue 1/2000 [CD-ROM]. Oxford/UK: Update Software, 2000
18. Dietzman RH, Lunseth JB, Goott B, et al. The use of methylprednisolone during cardiopulmonary bypass. A review of 427 cases. J Thorac Cardiovasc Surg 1975; 69: 870-3
19. Rokkanen P, Alho A, Avikainen V, et al. The efficacy of corticosteroids in severe trauma. Surg Gynecol Obstet 1974; 138: 69-73
20. Svennevig JL, Bugge-Asperheim B, Bjørgo S, et al. Methylprednisolone in the treatment of lung contusion following blunt chest trauma. Scand J Thorac Cardiovasc Surg 1980; 14: 301-5
21. Tønnesen E, Wanscher M, Höhndorf K, et al. Effect of methylprednisolone on the cytokine response in patients undergoing lung surgery. Acta Anaesthesiol Scand 1993; 37: 410-4
22. Schulze S, Moller IW, Bang U, et al. Effect of combined prednisolone, epidural analgesia and indomethacin on pain, systemic response and convalescence after cholecystectomy. Acta Chir Scand 1990; 156: 203-9
23. Høgevold HE, Aasen AO, Kierulf P, et al. High doses of corticosteroids in total hip replacement. Effects on components of coagulation, fibrinolytic, plasma kallikrein-kinin and complement systems. Acta Chir Scand 1989; 155: 247-50
24. Hammerschmidt DE, White JG, Craddock PR, et al. Corticosteroids inhibit complement-induced granulocyte aggregation. A possible mechanism for their efficacy in shock states. J Clin Invest 1979; 63: 798-803
25. Barber AE, Coyle SM, Fischer E, et al. Influence of hypercortisolemia on soluble tumor necrosis factor receptor II and interleukin-1 receptor antagonist responses to endotoxin in human beings. Surgery 1995; 118: 406-11
26. Moore PK, Hoult JR. Anti-inflammatory steroids reduce tissue PG synthetase activity and enhance PG breakdown. Nature 1980; 288: 269-70
27. Korman B, McKay RJ. Steroids and postoperative analgesia. Anaesth Intens Care 1985; 13: 395-8
28. Neugebauer E, Dietrich A, Bouillon B, et al. Steroids in trauma patients-right or wrong? A qualitative meta-analysis of clinical studies. Theor Surg 1990; 5: 44-53
29. Beckmann J. Basic aspects of risk-benefit analysis. Semin Thromb Hemost 1999; 25: 89-95
30. Edwards R, Wiholm BE, Martinez C. Concepts in risk-benefit assessment. A simple merit analysis of a medicine? Drug Saf 1996; 15: 1-7
31. Krantz T, Wolff C, Hjortso NC, et al. Assessment of early postoperative convalescence by a simple scoring system [in Danish]. Ugeskr Laeger 1990; 152: 1168-70
32. Bigler D, Jonsson T, Olsen J, et al. The effect of preoperative methylprednisolone on pulmonary function and pain after lung operations. J Thorac Cardiovasc Surg 1996; 112: 142-5
33. Komori K, Ishida M, Matsumoto T, et al. Cytokine patterns and the effects of a preoperative steroid treatment in the patients with abdominal aortic aneurysms. Int Angiol 1999; 18: 193-7
34. Launo C, Palermo S, Gobbi GC, et al. Methylprednisolone sodium succinate versus placebo in the prevention of respiratory complications after thoracic surgery [In Italian]. Minerva Anestesiol 1990; 56: 219-23
35. Nagelschmidt M, Fu ZX, Saad S, et al. Preoperative high dose methylprednisolone improves patients outcome after abdominal surgery. Eur J Surg 1999; 165: 971-8
36. Schulze S, Andersen J, Overgaard H, et al. Effect of prednisolone on the systemic response and wound healing after colonic surgery. Arch Surg 1997; 132: 129-35
37. Sumida M, Inaba H, Isawa E, et al. Prevention by methylprednisolone of increased circulating tumor necrosis factor-alpha levels and lung injury associated with systemic inflammatory response syndrome due to intraperitoneal hyperthermia. Anesth Analg 1999; 88: 771-6
38. Takeda S, Ogawa R, Nakanishi 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
39. Zotti GC, Salzano de Luna F, Caiazza A, et al. Prevention of pulmonary complications by 6-methylprednisolone in major abdominal surgery. Ital J Surg Sci 1988; 18: 369-75
40. Chaney MA, Nikolov MP, Blakeman B, et al. Pulmonary effects of methylprednisolone in patients undergoing coronary artery bypass grafting and early tracheal extubation. Anesth Analg 1998; 87: 27-33
41. Chaney MA, Nikolov MP, Blakeman BP, et al. Hemodynamic effects of methylprednisolone in patients undergoing cardiac operation and early extubation. Ann Thorac Surg 1999; 67: 1006-11

42. Engelman RM, Rousou JA, Flack JE, 3rd, et al. Influence of steroids on complement and cytokine generation after cardiopulmonary bypass. Ann Thorac Surg 1995; 60: 801-4
43. Fecht DC, Magovern GJ, Park SB, et al. Beneficial effects of methylprednisolone in patients on cardiopulmonary bypass. Circ Shock 1978; 5: 415-22
44. Niazi Z, Flodin P, Joyce L, et al. Effects of glucocorticosteroids in patients undergoing coronary artery bypass surgery. Chest 1979; 76: 262-8
45. Tassani P, Richter JA, Barankay A, et al. Does high-dose methylprednisolone in aprotinin-treated patients attenuate the systemic inflammatory response during coronary artery bypass grafting procedures? J Cardiothorac Vasc Anesth 1999; 13: 165-72
46. Otani K, Abe H, Kadoya S, et al. Beneficial effect of methylprednisolone sodium succinate in the treatment of acute spinal cord injury [In Japanese]. Spine and Spinal Cord 1994; 7: 633-47
47. Otani K. Treatment effect of methylprednisolone sodium succinate in acute cervical spinal cord injury [in Japanese]. J Jpn Med Soc Parapl 1995; 8: 80-1
48. Petitjean ME, Pointillart V, Dixmerias F, et al. Pharmacological therapy of spinal cord injury at the acute phase [In French]. Ann Fr Anesth Réanim 1998; 17: 114-22
49. Pointillart V, Petitjean ME, Wiart L, et al. Pharmacological therapy of spinal cord injury during the acute phase. Spinal Cord 2000; 38: 71-6
50. Pettersson K, Toolanen G. High-dose methylprednisolone prevents extensive sick leave after whiplash injury. A prospective, randomized, double-blind study. Spine 1998; 23: 984-9
51. Høgevold HE, Hoiseth A, Reikerås O. Effect of high-dose corticosteroids on the incidence of deep vein thrombosis after total hip replacement. Arch Orthop Trauma Surg 1991; 111: 29-31
52. Høgevold HE, Mundal HH, Norman N, et al. Platelet release reaction and plasma catecholamines during total hip replacement. No effects of high doses of corticosteroids. Thromb Res 1990; 57: 21-9
53. Gammer W, Bengtson A, Heideman M. Inhibition of complement activation by high-dose corticosteroids in total hip arthroplasty. Clin Orthop 1988; 236: 205-9
54. Andersen LW, Baek L, Thomsen BS, et al. Effect of methylprednisolone on endotoxemia and complement activation during cardiac surgery. J Cardiothorac Anesth 1989; 3: 544-9
55. Jansen NJ, van Oeveren W, van Vliet M, et al. The role of different types of corticosteroids on the inflammatory mediators in cardiopulmonary bypass. Eur J Cardiothorac Surg 1991; 5: 211-7
56. Mayumi H, Zhang QW, Nakashima A, et al. Synergistic immunosuppression caused by high-dose methylprednisolone and cardiopulmonary bypass. Ann Thorac Surg 1997; 63: 129-37
57. Morton JR, Hiebert CA, Lutes CA, et al. Effect of methylprednisolone on myocardial preservation during coronary artery surgery. Am J Surg 1976; 131: 419-22
58. Toft P, Christiansen K, Tønnesen E, et al. Effect of methylprednisolone on the oxidative burst activity, adhesion molecules and clinical outcome following open heart surgery. Scand Cardiovasc J 1997; 31: 283-8
59. Toledo-Pereyra LH, Lin CY, Kundler H, et al. Steroids in heart surgery: a clinical double-blind and randomized study. Am Surg 1980; 46: 155-60
60. Rao G, King J, Ford W, et al. The effects of methylprednisolone on the complications of coronary artery surgery. Vasc Surg 1977; 11: 1-7
61. Wan S, LeClerc JL, Schmartz D, et al. Hepatic release of interleukin-10 during cardiopulmonary bypass in steroid-pretreated patients. Am Heart J 1997; 133: 335-9
62. Wan S, LeClerc JL, Huynh CH, et al. Does steroid pretreatment increase endotoxin release during clinical cardiopulmonary bypass? J Thorac Cardiovasc Surg 1999; 117: 1004-8
63. Alho A, Saikku K, Eerola P, et al. Corticosteroids in patients with a high risk of fat embolism syndrome. Surg Gynecol Obstet 1978; 147: 358-62
64. Lepistö P, Avikainen V, Alho A, et al. Fat embolism in severely injured patients. Ann Chir Gynaecol Fenn 1975; 64: 198-202
65. Lindeque BGP, Schoeman HS, Dommisse GF, et al. Fat embolism and the fat embolism syndrome. A double-blind therapeutic study. J Bone Joint Surg Br 1987; 69: 128-31
66. Schonfeld SA, Ploysongsang Y, DiLisio R, et al. Fat embolism prophylaxis with corticosteroids. A prospective study in high-risk patients. Ann Intern Med 1983; 99: 438-43
67. Stoltenberg JJ, Gustilo RB. The use of methylprednisolone and hypertonic glucose in the prophylaxis of fat embolism syndrome. Clin Orthop 1979; 143: 211-21
68. Svennevig JL, Bugge-Asperheim B, Vaage J, et al. Corticosteroids in the treatment of blunt injury of the chest. Injury 1984; 16: 80-4
69. Svennevig JL, Bugge-Asperheim B, Geiran O, et al. High-dose corticosteroids in thoracic trauma. Acta Chir Scand Suppl 1985; 526: 110-9
70. Svennevig JL, Bugge-Asperheim B, Birkeland S, et al. Efficacy of steroids in the treatment of lung contusion. Acta Chir Scand Suppl 1980; 499: 87-92
71. Mikawa K, Ikegaki J, Maekawa N, et al. Perioperative effect of methylprednisolone given during lung surgery on plasma concentrations of C3a and C5a. Scand J Thorac Cardiovasc Surg 1990; 24: 229-33
72. Edfeldt H, Thomson D. Early hemodynamic and respiratory changes following tourniquet release - influence of large doses of methylprednisolone. Acta Chir Scand Suppl 1980; 499: 45-55
73. Boscoe MJ, Yewdall VM, Thompson MA, et al. Complement activation during cardiopulmonary bypass: quantitative study of effects of methylprednisolone and pulsatile flow. BMJ 1983; 287: 1747-50
74. Diego RP, Mihalakakos PJ, Hexum TD, et al. Methylprednisolone and full-dose aprotinin reduce reperfusion injury after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 1997; 11: 29-31
75. Enderby DH, Boylett A, Parker DJ. Methyl prednisolone and lung function after cardiopulmonary bypass. Thorax 1979; 34: 720-5
76. Ferries LH, Marx Jr JJ, Ray III JF. The effect of methylprednisolone on complement activation during cardiopulmonary bypass. J Extracorp Technol 1984; 16: 83-8
77. Fosse E, Mollnes TE, Østerud A, et al. Effects of methylprednisolone on complement activation and leukocyte counts during cardiopulmonary bypass. Scand J Thorac Cardiovasc Surg 1987; 21: 255-61
78. Hill GE, Alonso A, Thiele GM, et al. Glucocorticoids blunt neutrophil CD11b surface glycoprotein upregulation during cardiopulmonary bypass in humans. Anesth Analg 1994; 79: 23-7
79. Hill GE, Alonso A, Spurzem JR, et al. Aprotinin and methylprednisolone equally blunt cardiopulmonary bypass- induced inflammation in humans. J Thorac Cardiovasc Surg 1995; 110: 1658-62

80. Jorens PG, De Jongh R, De Backer W, et al. Interleukin-8 production in patients undergoing cardiopulmonary bypass. The influence of pretreatment with methylprednisolone. Am Rev Respir Dis 1993; 148: 890-5
81. Karlstad MD, Patteson SK, Guszcza JA, et al. Methylprednisolone does not influence endotoxin translocation during cardiopulmonary bypass. J Cardiothorac Vasc Anesth 1993; 7: 23-7
82. Kawamura T, Inada K, Nara N, et al. Influence of methylprednisolone on cytokine balance during cardiac surgery. Crit Care Med 1999; 27: 545-8
83. Kawamura T, Inada K, Okada H, et al. Methylprednisolone inhibits increase of interleukin 8 and 6 during open heart surgery. Can J Anaesth 1995; 42: 399-403
84. Kobayashi N. The circulatory and respiratory effects of methylprednisolone associated with catecholamine undergoing open heart surgery [In Japanese]. Tokyo Joshi Ikadaigaku Zasshi [Journal of Tokyo Womens Medical College] 1996; 66: 1-10
85. Loubser PG, Yawn D. Effects of methylprednisolone on complement activation during cardiopulmonary bypass and following protamine administration [abstract]. Anesthesiology 1994; 81: A173
86. Loubser PG. Effect of methylprednisolone on complement activation during heparin neutralization. J Cardiovasc Pharmacol 1997; 29: 23-7
87. Tabardel Y, Duchateau J, Schmartz D, et al. Corticosteroids increase blood interleukin-10 levels during cardiopulmonary bypass in men. Surgery 1996; 119: 76-80
88. Thompson MA, Broadbent MP. Methylprednisolone prior to cardiopulmonary bypass. Anaesthesia 1980; 35: 345-53
89. Thompson MA, Broadbent MP, English J. Plasma levels of methylprednisolone following administration during cardiac surgery. Anaesthesia 1982; 37: 405-7
90. Deeks J, Bradburn M, Localio R, et al. Much ado about nothing: statistical methods for meta-analysis with rare events [abstract]. 2nd Symposium on Systematic Reviews. 1999 Jan 8-9; Oxford, 31
91. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. BMJ 1995; 310: 452-4
92. Dernek S, Tünerir B, Sevin B, et al. The effects of methylprednisolone on complement, immunoglobulins and pulmonary neutrophil sequestration during cardiopulmonary bypass. Cardiovasc Surg 1999; 7: 414-8
93. Shimada M, Saitoh A, Kano T, et al. The effect of a perioperative steroid pulse on surgical stress in hepatic resection. Int Surg 1996; 81: 49-51
94. Teoh KH, Bradley CA, Gauldie J, et al. Steroid inhibition of cytokine-mediated vasodilation after warm heart surgery. Circulation 1995; 92 Supple. 2: S347-S353
95. van der Merwe CJ, Louw AF, Welthagen D, et al. Adult respiratory distress syndrome in cases of severe trauma-the prophylactic value of methylprednisolone sodium succinate. S Afr Med J 1985; 67: 279-84
96. Lee CW, Chae JK, Lim HY, et al. Prospective randomized trial of corticosteroids for the prevention of restenosis after intracoronary stent implantation. Am Heart J 1999; 138: 60-3
97. Pepine CJ, Hirshfeld JW, Macdonald RG, et al. A controlled trial of corticosteroids to prevent restenosis after coronary angioplasty. M-HEART Group. Circulation 1990; 81: 1753-61
98. Flood TR, McManners J, El-Attar A, et al. Randomized prospective study of the influence of steroids on postoperative eye-opening after exploration of the orbital floor. Br J Oral Maxillofac Surg 1999; 37: 312-5
99. Holland CS. The influence of methylprednislone on post-operative swelling following oral surgery. Br J Oral Maxillofac Surg 1987; 25: 293-9
100. Butler J, Pathi VL, Paton RD, et al. Acute-phase responses to cardiopulmonary bypass in children weighing less than 10 kilograms. Ann Thorac Surg 1996; 62: 538-42
101. Westfall SH, Stephens C, Kesler K, et al. Complement activation during prolonged extracorporeal membrane oxygenation. Surgery 1991; 110: 887-91
102. Kallenbach J, Lewis M, Zaltzman M, et al. 'Low-dose' corticosteroid prophylaxis against fat embolism. J Trauma 1987; 27: 1173-6
103. Matsutani T, Onda M, Sasajima K, et al. Glucocorticoid attenuates a decrease of antithrombin III following major surgery. J Surg Res 1998; 79: 158-63
104. Rendina EA, Venuta F, Ricci C. Effects of low-dose steroids on bronchial healing after sleeve resection. A clinical study. J Thorac Cardiovasc Surg 1992; 104: 888-91
105. Peillon D, Dubost J, Roche C, et al. Effect of corticosteroids and haemodilution on postoperative inflammation after maxillofacial surgery. Ann Fr Anesth Réanim 1996; 15: 157-61
106. Owsley JQ, Weibel TJ, Adams WA. Does steroid medication reduce facial edema following face lift surgery? A prospective, randomized study of 30 consecutive patients. Plast Reconstr Surg 1996; 98: 1-6
107. Marion DW, Jannetta PJ. Use of perioperative steroids with microvascular decompression operations. Neurosurgery 1988; 22: 353-7
108. Williams PM, Strome M, Eliachar I, et al. Impact of steroids on recovery after uvulopalatopharyngoplasty. Laryngoscope 1999; 109: 1941-6
109. Bouillon B, Krämer M, Schäfer U, et al. High dose corticosteroids in patients with multiple trauma [abstract]. Shock 1996; 5 Suppl. 2: S45
110. Muñoz C, Conejero R, Caturla J, et al. Inhibition of cytokine production in cardiopulmonary bypass [abstract]. Clin Intens Care 1992; 3 Suppl.: S52
111. Schulze S, Sommer P, Bigler D, et al. Effect of combined prednisolone, epidural analgesia, and indomethacin on the systemic response after colonic surgery. Arch Surg 1992; 127: 325-31
112. Vallejo JL, Gimenez-Fernandez R, Mainer JL, et al. Análisis clínico del efecto protector de la metil-prednisolona sobre el corazón en paro anóxico (estudio randomizado). Rev Esp Cardiol 1977; 30: 705-9
113. Fu ZX, Nagelschmidt M, Saad S, et al. Improved outcome by preoperative administration of methylprednisolone before large abdominal surgery interventions-a prospective double-blind study [in German]. Langenbecks Arch Chir Suppl Kongressbd 1997; 114: 663-6
114. Derendorf H, Möllmann H, Krieg M, et al. Pharmacodynamics of methylprednisolone phosphate after single intravenous administration to healthy volunteers. Pharm Res 1991; 8: 263-8
115. Novak E, Stubbs SS, Seckman CE, et al. Effects of a single large intravenous dose of methylprednisolone sodium succinate. Clin Pharmacol Ther 1970; 11: 711-7
116. Eypasch E, Lefering R, Kum CK, et al. Probability of adverse events that have not yet occurred: a statistical reminder. BMJ 1995; 311: 619-20
117. Conn HO, Blitzer BL. Nonassociation of adrenocorticosteroid therapy and peptic ulcer. N Engl J Med 1976; 294: 473-9
118. McIntyre PB, Berkey CS, King SM, et al. Dexamethasone as adjunctive therapy in bacterial meningitis. A meta-analysis of randomized clinical trials since 1988. JAMA 1997; 278: 925-31

119. Dumouchel W. Meta-analysis for dose-response models. Stat Med 1995; 14: 679-85
120. DeMaria EJ, Reichman W, Kenney PR, et al. Septic complications of corticosteroid administration after central nervous system trauma. Ann Surg 1985; 202: 248-52
121. Galandiuk S, Raque G, Appel S, et al. The two-edged sword of large-dose steroids for spinal cord trauma. Ann Surg 1993; 218: 419-27
122. Gerndt SJ, Rodriguez JL, Pawlik JW, et al. Consequences of high-dose steroid therapy for acute spinal cord injury. J Trauma 1997; 42: 279-84
123. Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. BMJ 1998; 317: 1185-90
124. Bocanegra TS, Castañeda MO, Espinoza LR, et al. Sudden death after methylprednisolone pulse therapy [letter]. Ann Intern Med 1981; 95: 122
125. Moses RE, McCormick A, Nickey W. Fatal arrhythmia after pulse methylprednisolone therapy. Ann Intern Med 1981; 95: 781-2
126. Guillen EL, Ruiz AM, Bugallo JB. Hypotension, bradycardia, and asystole after high-dose intravenous methylprednisolone in a monitored patient [letter]. Am J Kidney Dis 1998; 32: E4
127. Tvede N, Nielsen LP, Andersen V. Bradycardia after high-dose intravenous methylprednisolone therapy. Scand J Rheumatol 1986; 15: 302-4
128. Lewis DA, Smith RE. Steroid-induced psychiatric syndromes. A report of 14 cases and a review of the literature. J Affect Disord 1983; 5: 319-32
129. Olsen R, Lindberg C, Anderson O. Centrolobular liver cell necrosis, myocardial infarction, and hyperamylasaemia after high dose corticosteroids [letter]. BMJ 1994; 308: 454
130. Smith RS, Warren DJ. Effects of high-dose intravenous methylprednisolone on circulation in humans. Transplantation 1983; 35: 349-51
131. Schonwald S. Methylprednisolone anaphylaxis. Am J Emerg Med 1999; 17: 583-5
132. Schulz KF, Chalmers I, Hayes RH, et al. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995; 273: 408-12
133. Plihal W, Krug R, Pietrowsky R, et al. Corticosteroid receptor mediated effects on mood in humans. Psychoneuroendocrinology 1996; 21: 515-23
134. Patten SB, Neutel SI. Corticosteroid-induced adverse psychiatric effects: incidence, diagnosis and management. Drug Saf 2000; 22: 111-22
135. Felson DT, Anderson JJ. Across-study evaluation of association between steroid dose and bolus steroids and avascular necrosis of bone. Lancet 1987; I: 902-6

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