



Effect of dexamethasone on complications or all cause mortality after major non-cardiac surgery: multicentre, double blind, randomised controlled trial

Karim Asehnoune, Charlene Le Moal, Gilles Lebuffe, Marguerite Le Penndu, Nolwen Chatel Josse, Matthieu Boisson, Thomas Lescot, Marion Faucher, Samir Jaber, Thomas Godet, et al.

► To cite this version:

Karim Asehnoune, Charlene Le Moal, Gilles Lebuffe, Marguerite Le Penndu, Nolwen Chatel Josse, et al.. Effect of dexamethasone on complications or all cause mortality after major non-cardiac surgery: multicentre, double blind, randomised controlled trial. BMJ - British Medical Journal, 2021, 373, pp.n1162. 10.1136/bmj.n1162 . hal-03258675

HAL Id: hal-03258675

<https://hal.science/hal-03258675>

Submitted on 12 Jun 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Effect of dexamethasone on complications or all cause mortality after major non-cardiac surgery: multicentre, double blind, randomised controlled trial

Karim Asehnoune,¹ Charlene Le Moal,² Gilles Lebuffe,³ Marguerite Le Penndu,¹ Nolwen Chatel Josse,⁴ Matthieu Boisson,⁵ Thomas Lescot,⁶ Marion Faucher,⁷ Samir Jaber,⁸ Thomas Godet,⁹ Marc Leone,¹⁰ Cyrus Motamed,¹¹ Jean Stephane David,¹² Raphael Cinotti,¹³ Younes El Amine,¹⁴ Darius Liutkus,² Matthias Garot,³ Antoine Marc,¹ Anne Le Corre,⁴ Alexandre Thomasseau,⁵ Alexandra Jobert,¹⁵ Laurent Flet,¹⁶ Fanny Feuillet,¹⁷ Morgane Pere,¹⁵ Emmanuel Futier,⁹ Antoine Roquilly,¹ on behalf of the PACMAN study group

For numbered affiliations see end of the article.

Correspondence to: K Asehnoune karim.asehnoune@chu-nantes.fr (ORCID 0000-0003-1899-3517)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2021;373:n1162 <http://dx.doi.org/10.1136/bmj.n1162>

Accepted: 5 May 2021

ABSTRACT OBJECTIVE

To assess the effect of dexamethasone on complications or all cause mortality after major non-cardiac surgery.

DESIGN

Phase III, randomised, double blind, placebo controlled trial.

SETTING

34 centres in France, December 2017 to March 2019.

PARTICIPANTS

1222 adults (>50 years) requiring major non-cardiac surgery with an expected duration of more than 90 minutes. The anticipated time frame for recruitment was 24 months.

INTERVENTIONS

Participants were randomised to receive either dexamethasone (0.2 mg/kg immediately after the surgical procedure, and on day 1) or placebo. Randomisation was stratified on the two prespecified criteria of cancer and thoracic procedure.

MAIN OUTCOMES MEASURES

The primary outcome was a composite of postoperative complications or all cause mortality within 14 days after surgery, assessed in the modified intention-to-treat population (at least one treatment administered).

RESULTS

Of the 1222 participants who underwent randomisation, 1184 (96.9%) were included in the

modified intention-to-treat population. 14 days after surgery, 101 of 595 participants (17.0%) in the dexamethasone group and 117 of 589 (19.9%) in the placebo group had complications or died (adjusted odds ratio 0.81, 95% confidence interval 0.60 to 1.08; $P=0.15$). In the stratum of participants who underwent non-thoracic surgery ($n=1038$), the primary outcome occurred in 69 of 520 participants (13.3%) in the dexamethasone group and 93 of 518 (18%) in the placebo group (adjusted odds ratio 0.70, 0.50 to 0.99). Adverse events were reported in 288 of 613 participants (47.0%) in the dexamethasone group and 296 of 609 (48.6%) in the placebo group ($P=0.46$).

CONCLUSIONS

Dexamethasone was not found to significantly reduce the incidence of complications and death in patients 14 days after major non-cardiac surgery. The 95% confidence interval for the main result was, however, wide and suggests the possibility of important clinical effectiveness.

TRIAL REGISTRATION

ClinicalTrials.gov NCT03218553.

Introduction

More than 300 million major surgical procedures are undertaken each year worldwide.¹ In a European survey, the mortality rate after non-cardiac surgery was much higher than expected,² and important complications developed in 15% to 25% of patients during hospital admission.^{3 4} Moreover, the impact of postoperative complications on functional status and long term survival is high. As 10% of patients at risk represent 80% of postoperative deaths,⁵ approaches targeting high risk patients that even modestly decrease the rate of postoperative complications would considerably improve the long term outcomes of surgical patients and would also lower costs.

Major surgery induces both local and systemic inflammation.⁶ This inflammatory response is a prerequisite for tissue healing, but if it is overwhelmed then remote organ failure or secondary infections can occur.⁷ In this setting, glucocorticoids could be an option, especially given that these molecules have been associated with improved outcomes in medical conditions characterised by systemic inflammatory response, such as septic shock or severe trauma.⁸⁻¹⁰

WHAT IS ALREADY KNOWN ON THIS TOPIC

Patients who undergo major surgery are particularly at risk of organ failure from inflammatory origin

In a recent meta-analysis of major abdominal surgery, perioperative use of corticosteroids was associated with a significantly decreased risk of complications

WHAT THIS STUDY ADDS

Compared with placebo, dexamethasone administered postoperatively at higher dose than the usual antiemetic dose was not associated with a reduction in complications or mortality 14 days after surgery

Use of dexamethasone appeared to be safe

Confidence intervals were, however, wide, and therefore suggests the possibility of important clinical effectiveness

In patients undergoing cardiopulmonary surgery, however, the use of steroids has been associated with an increased risk of myocardial injury, and the effects on atrial fibrillation and postoperative infections remain uncertain.¹¹⁻¹³

Most studies have investigated the effects on the risk of perioperative nausea of one injection of 4-8 mg of dexamethasone administered before surgery.¹⁴ Meta-analyses have concluded that evidence is lacking to show a clear clinical benefit of dexamethasone other than on nausea and vomiting or to rule out major clinical side effects.^{15 16} We hypothesised that a higher dose of dexamethasone could help to safely prevent inflammation related postoperative complications. We conducted the Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac surgery (PACMAN) phase III randomised controlled trial to assess the effect of dexamethasone on postoperative complications in adults older than 50 years who underwent major non-cardiac surgery.

Methods

Trial design and setting

We conducted a pragmatic, investigator initiated, multicentre, parallel group, double blind, randomised controlled trial to compare dexamethasone with placebo in patients considered at risk of complications after major non-cardiac surgery. Patients provided written informed consent before participation. The study protocol and statistical analysis plan were submitted before the inclusion of participants and were published before the end of enrolment.¹⁷ The department of research at the University hospital of Nantes conducted data monitoring and quality checks. Investigators reported any adverse events within seven days. An independent data and safety monitoring board regularly monitored patient safety and analysed adverse event reports in a blinded manner. All study endpoints were collected and analysed blindly.

The trial was conducted in 34 French hospitals (26 university hospitals, 4 general hospitals, 2 cancer institutes, and 2 private hospitals; see supplementary table A). Patients older than 50 years with at least one risk factor for postoperative complications¹⁸ or older than 65 years and who were to undergo major non-cardiac surgery planned to last 90 minutes or more were eligible for enrolment. The supplementary file provides complete lists of inclusion and exclusion criteria; see study protocol (supplementary table B).

An independent research unit at the University Hospital of Nantes performed the randomisation. A statistician randomised the participants using a computer generated random number in fixed blocks of 6 (1:1 ratio). Stratification was based on surgery for cancer (yes or no) and on intrathoracic surgery (yes or no), both of which are major risk factors for postoperative respiratory complications.¹⁸ Before surgery was performed, local investigators randomised enrolled participants using a dedicated, password protected, SSL encrypted website (CSOnline; Clinsight) to allow immediate and concealed allocation. At each

participating centre, the pharmacist delivered the study drugs, which were then administered by clinical nurses unaware of the treatment groups. Treatment assignment was concealed from participants and site investigators.

Intervention

The study drug, dexamethasone phosphate 20 mg/5 mL vials (Mylan; Saint-Priest, France), and placebo were indiscernible. Supplementary table C describes the blinding process for the experimental drugs.

Participants received dexamethasone 0.2 mg per kilogram of actual body weight (dexamethasone group) or matching placebo (placebo group) as a bolus immediately after surgery (<2 hours after skin closure) and on day 1 after surgery. The maximum daily dose was 20 mg.

All other interventions were at the discretion of the clinicians. For consistency, timely antimicrobial prophylaxis,¹⁹ use of low tidal volume and positive end expiratory pressure during surgery,²⁰ treatment of perioperative hypotension,²¹ and early discontinuation of sedation after the procedure²² were required. In patients with diabetes, blood glucose levels were measured every 2-3 hours for the first three days, then twice daily for two days, and thereafter the insulin dose was adapted accordingly. Blood levels of troponins in participants considered at risk of postoperative cardiac events were measured according to local procedure. Prophylactic use of glucocorticoids for postoperative nausea and vomiting or postoperative oedema was prohibited. Glucocorticoids were allowed as rescue treatment in case of urgent indications, such as stridor or asthma exacerbation.

Outcomes

Supplementary table D provides definitions for the outcomes of interest. The primary outcome was a composite of complications and all cause mortality 14 days after surgery. Postoperative complications were sepsis and pneumonia, defined according to consensus criteria,²³ and the need for invasive or non-invasive mechanical ventilation for acute respiratory failure.^{20 24} Each of these outcomes was also analysed separately. Sepsis was defined as life threatening organ dysfunction caused by an infection.²³ Organ dysfunction was identified as an acute change in total sequential organ failure assessment (SOFA) score of ≥ 2 points owing to infection. Infection was indicated by an organism identified from blood culture or from a sterile site, or an abscess or infected tissue (eg, pneumonia, peritonitis, urinary tract, vascular line infection, soft tissue).

Secondary outcomes were all cause mortality at 28 days, rates of postoperative complications within 28 days (defined according to the Clavien-Dindo classification), renal and respiratory failures within 14 days after surgery, sequential organ failure assessment score on postoperative days 1 and 3, total duration of invasive and non-invasive mechanical ventilation, lengths of stay in the intensive care unit (ICU) and in

hospital, and the percentage of patients with adverse events on day 28. C reactive protein concentration was measured after surgery immediately before the first injection of the study treatment, then on days 1 and 2 after surgery.

Analysis

The rate of the primary outcome ranged from 15% to 25% in recent studies.^{3 4 20 24} In studies including participants at high risk of postoperative complications, dexamethasone was associated with a relative reduction in mortality of 20%,²⁵ respiratory complications of 31% to 53%,¹⁴ and wound infection of 20%.¹⁶ We thus hypothesised that dexamethasone would be associated with a relative reduction of 30% in the rate of our composite primary outcome. Assuming a rate of 20% in the control group and 14% in the dexamethasone group, we calculated that a total of 1222 patients (611 patients in each group) would be needed to detect this difference with a 5% type I error and a power of 80% in a two sided test.

Analyses were performed using SAS software (version 9.4, NC) before the breaking of the randomisation code. The figures were made with R version 3.6.1. software. Type I error (α) was set at 5%.

The main analysis of the primary outcome was conducted in the modified intention-to-treat population,¹⁷ defined as all randomised participants except those who would have no longer been considered eligible for randomisation at the time of first treatment injection or who would never had any injection of the study treatment. We also analysed the primary outcome in the intention-to-treat population, defined as all randomised participants, and finally in the per protocol population, defined as all randomised participants except those with one or more major protocol violations (not eligible for randomisation, received the wrong intervention, surgical intervention was not performed, consent was withdrawn, or received out-of-protocol glucocorticoids). Since data were missing for the primary outcome, we analysed the intention-to-treat population with multiple imputation methods using personal data (age, sex), stratification factors, preoperative biological data, and type of surgery (five imputed datasets).

In the adjusted analyses, we used a logistic regression model that included a fixed effect for stratification factors (cancer, intrathoracic procedure) and centre as a random effect. Kaplan-Meier plots were used to show the rate of events in a time-to-event analysis, and differences were tested using a Cox model adjusted on stratification factors and centre as random effect and censored at 14 days after surgery. Independent components of the primary outcome (other than death) were analysed with Fine and Gray models adjusted on stratification factors, and centre as random effect with death considered as a competing risk. For analysis of the prespecified subgroups, we calculated the odds ratios with 95% confidence intervals without multiple adjustment. The direction effect across the subgroups was not a priori indicated in the protocol.

Analyses of secondary outcomes were conducted on data from the modified intention-to-treat population and took into account stratified randomisation and centre as random effect. Continuous variables are presented as means and standard deviations or as medians and interquartile ranges, and categorical data are presented as numbers and percentages. Missing data are described by treatment arm.

Categorical data (eg, the proportion of patients who experienced adverse events, postoperative morbidity, primary outcome) were analysed with logistic regression adjusted for stratification factors as fixed effect and centre as a random effect. Ordinal categorical data (infection severity and Clavien-Dindo classification) were analysed with ordinal logistic regression adjusted for stratification factors. Longitudinal continuous data were analysed with linear mixed models, with random effects models adjusted for stratification factors to account for repeated measurements. Assumptions of normality and homoscedasticity associated with these models were evaluated. The duration of mechanical ventilation and stays in the ICU and hospital were analysed using competing risk models to take into account informative censoring and competing risk owing to death.

Patient and public involvement

Except for providing written informed consent before participation, no patients or members of the public were involved in the research, mainly because of funding restrictions. Although patients and the public were not directly involved in the study, we did speak to patients about the study and we asked a member of the public to read our manuscript before submission.

Results

From December 2017 to March 2019, 1222 participants were randomised (613 in the dexamethasone group and 609 in the placebo group; fig 1). No unblinding occurred, and 13 of 1222 participants (1.1%) received dexamethasone outside of the study protocol. After excluding 38 participants (did not meet the inclusion criteria, did not receive any injection of the experimental treatment, or withdrew consent), 595 participants in the dexamethasone group and 589 in the placebo group met the criteria for the modified intention-to-treat population. Thirty eight of 1222 participants (3.1%) had major protocol violations (received the wrong intervention, no surgical intervention was performed, or withdrew consent) but were kept in the modified intention-to-treat analysis (see supplementary table E for protocol dropouts). Table 1 shows the baseline characteristics of the participants. Most types of surgery were represented. Clinical care outside the trial intervention, including antimicrobial prophylaxis, haemodynamic support, and perioperative ventilatory support, complied with the international standard of care recommendations.

In the modified intention-to-treat analysis, 1184 of 1222 participants (96.9%) were analysed. Overall, 101 of 595 participants (17.0%) in the dexamethasone

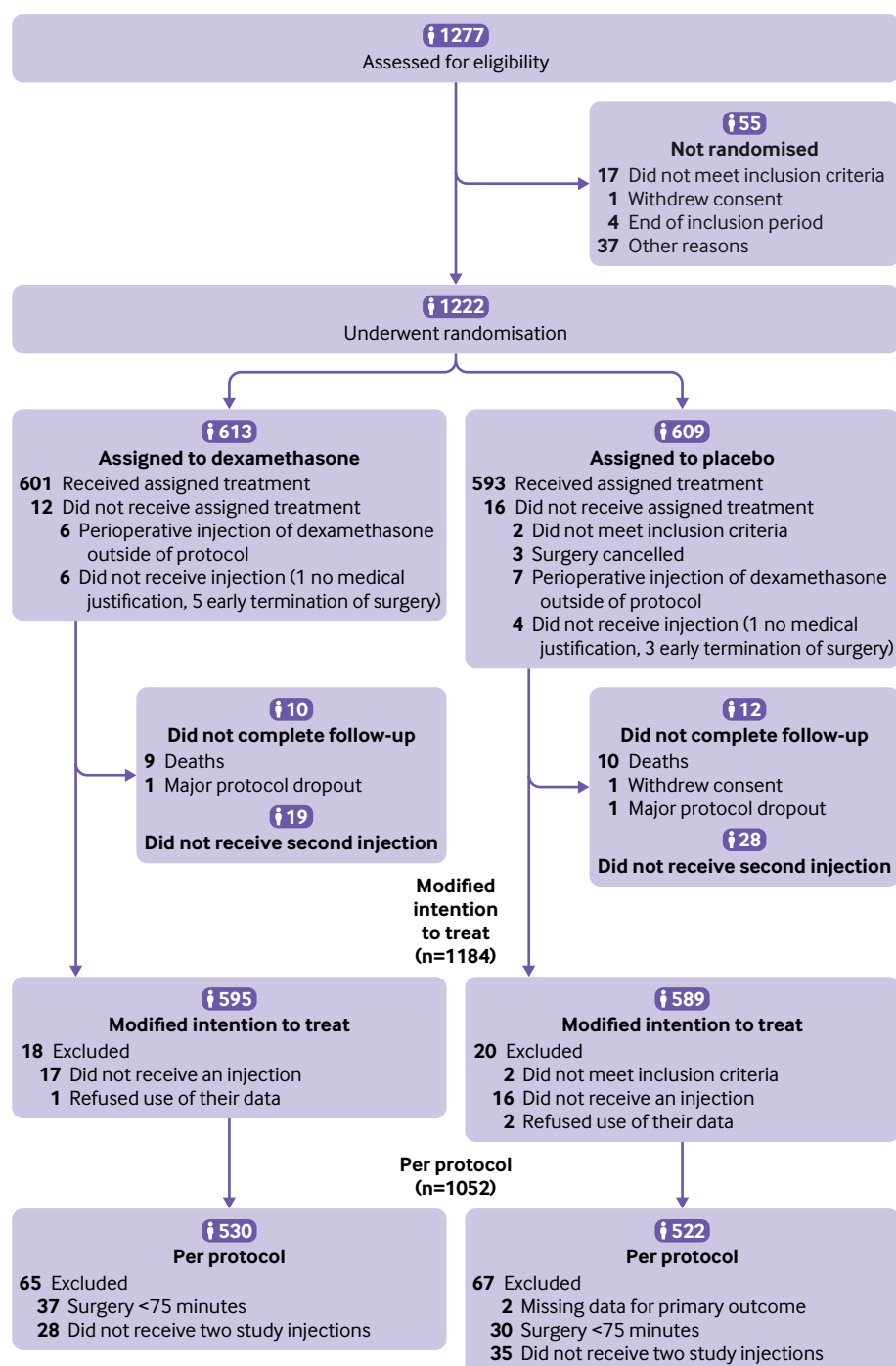


Fig 1 | Flow of participants through study

group and 117 of 589 (19.9%) in the placebo group had died or developed complications 14 days after surgery (adjusted odds ratio 0.81, 95% confidence interval 0.60 to 1.08; $P=0.15$, table 2). The adjusted hazard ratio for the composite of postoperative complications and all cause mortality with dexamethasone was 0.74 (0.64 to 1.09; $P=0.18$, see supplementary fig A). Supplementary figure B shows the range of sample sizes across centres, and the centre specific estimates of odd ratios for the primary outcome with dexamethasone.

In the a priori defined randomisation stratum of participants who underwent non-thoracic surgery ($n=1038$), the composite of postoperative complications and all cause mortality occurred in 69 of 520 participants (13.3%) in the dexamethasone group and 93 of 518 (18.0%) in the placebo group (adjusted odds ratio 0.70, 0.50 to 0.99, fig 2). In the other a priori stratum of randomisation, dexamethasone was not associated with a change in risk of the primary outcome in participants who did or did not have surgery for cancer (0.79, 0.56 to 1.11 and 0.95, 0.47 to

Table 1 | Baseline characteristics of participants in modified intention-to-treat population. Values are numbers (percentages) unless stated otherwise

Characteristics	Total (n=1184)	Dexamethasone group (n=595)	Placebo group (n=589)
Median (interquartile range) age (years)	69 (65-74)	69 (65-74)	70 (65-74)
Men	748 (63.2)	377 (63.4)	371 (63)
Median (interquartile range) body mass index	26.2 (23.1-29.4)	26.1 (23.1-29.6)	26.3 (23.1-29.4)
Medical history:		n=560	n=561
Arterial hypertension	645 (57.5)	325 (58)	320 (57)
Diabetes mellitus	233 (20.8)	120 (21.4)	113 (20.1)
Cardiac insufficiency	67 (6)	36 (6.4)	31 (5.5)
Coronary heart disease	129 (11.5)	66 (11.8)	63 (11.2)
Chronic pulmonary disease	143 (12.8)	73 (13)	70 (12.5)
Chronic renal failure	81 (7.2)	37 (6.6)	44 (7.8)
Stroke	74 (6.6)	36 (6.4)	38 (6.7)
Current or former smoker	146 (13)	83 (14.8)	63 (11.2)
Malnutrition	89 (7.9)	40 (7.1)	49 (8.7)
Preoperative factors:		n=595	
Nutritional support	230 (19.4)	106 (17.8)	124 (19.4)
Chemotherapy	206 (17.4)	111 (18.7)	95 (16.1)
American Society of Anesthesiology score:		n=595	
I	80 (6.8)	33 (5.6)	47 (8)
II	713 (60.2)	367 (61.7)	346 (58.7)
III	380 (32.1)	190 (31.9)	190 (32.2)
IV	11 (0.9)	5 (0.8)	6 (1)
Median (interquartile range) blood test result at inclusion:		n=525	n=528
Leucocytes ($\times 10^9/L$)	7.9 (5.6-8.5)	7.9 (5.6-8.6)	7.4 (5.6-8.3)
Neutrophils ($\times 10^9/L$)	4.3 (3.2-5.5)	4.3 (3.2-5.7)	4.3 (5.2-5.3)
Lymphocytes ($\times 10^9/L$)	1.7 (1.3-2.2)	1.7 (1.2-2.3)	1.7 (1.3-2.1)
Creatinine ($\mu\text{mol/L}$)	73 (62-88)	73 (62-88)	73 (62-88)
Incision type:		n=595	n=589
Laparoscopy	381 (32.2)	196 (32.9)	185 (31.4)
Laparotomy	889 (75.1)	440 (74)	449 (76.2)
Surgery type:		n=595	
Cancer	774 (65.4)	385 (64.7)	389 (66)
Intrathoracic	146 (12.3)	75 (12.6)	71 (12.1)
Abdominal	752 (63.5)	385 (64.7)	367 (62.3)
Vascular	68 (5.7)	30 (5)	38 (6.5)
Orthopaedic	174 (14.7)	92 (15.5)	82 (13.9)
Neck or face	81 (6.8)	47 (7.9)	34 (5.8)
Antimicrobial prophylaxis	1056 (89.2)	541 (90.9)	515 (87.4)
No antimicrobial prophylaxis by surgery type:		n=595	
Cancer	96 (8.9)	39 (6.6)	57 (9.7)
Intrathoracic	5 (0.5)	1 (0.2)	4 (0.7)
Abdominal	61 (5.6)	28 (4.7)	33 (5.6)
Vascular	4 (0.4)	2 (0.3)	2 (0.3)
Orthopaedic	1 (0.1)	0 (0.0)	1 (0.2)
Neck or face	15 (1.4)	9 (1.5)	6 (1.0)
Warming blanket	1119 (94.5)	557 (93.6)	562 (95.4)
Mechanical ventilation during procedure:			
Median (interquartile range) tidal volume (mL)	470 (425-510)	470 (430-510)	470 (420-510)
Median (interquartile range) PEEP (cmH ₂ O)	5 (4-6)	5 (4-6)	5 (5-6)
Recruitment manoeuvre	593 (50.1)	295 (49.7)	298 (50.6)
Haemodynamic support:		n=595	
Stroke volume monitoring	203 (17.1)	98 (16.5)	105 (17.8)
Blood transfusion	110 (9.3)	50 (8.4)	60 (10.2)
Locoregional analgesia:		n=525	n=534
Spinal	63 (11.2)	35 (12)	28 (10.3)
Peridural	236 (41.8)	117 (40.2)	119 (43.6)
Perineural	121 (21.5)	58 (19.9)	63 (23.1)
Scar infiltration	150 (26.6)	85 (29.2)	65 (23.8)
Intraoperative complications:		n=595	n=589
Allergic reaction	85 (7.2)	41 (6.9)	44 (7.5)
Haemorrhagic shock	30 (2.5)	14 (2.3)	16 (2.7)
Organ perforation	7 (0.6)	3 (0.5)	4 (0.7)
Median (interquartile range) duration of surgery (mins)	188 (119-296)	195 (120-305)	180 (115-288)
Median (interquartile range) delay between skin closure and study treatment injection (mins)	10 (0-29)	10 (0-0.30)	10 (0-0.30)
Median (interquartile range) dose of dexamethasone or placebo (mg)	15 (13-17)	15 (13-17)	15 (13-17)

PEEP=positive end expiratory pressure.

1.88, respectively; fig 2). The effect of dexamethasone on risk of the primary outcome did not appear to be modified in any of the other prespecified subgroups, including duration of surgery, C reactive protein level on day 0, age, history of diabetes, site of incision, and surgery type (fig 2).

In the intention-to-treat analysis including all randomised participants, little change was found in the primary outcome (0.77, 0.57 to 1.05). Supplementary table F presents the analysis of participants with missing data. In the per protocol population, the adjusted odds ratio of the primary outcome with dexamethasone was 0.84 (0.61 to 1.16).

The mortality rate on day 14 was 1.0% (6 of 595 participants) in the dexamethasone group and 1.2% (7 of 589) in the placebo group; adjusted odds ratio with dexamethasone was 0.84 (0.52 to 1.38; table 2). The adjusted odds ratio for sepsis or pneumonia, or both, with dexamethasone was 0.82 (0.60 to 1.11) and the need for mechanical ventilation was 0.70 (0.53 to 0.93; table 2).

In the ordinal analyses for rates of complications using the Clavien-Dindo classification, no differences were found between the two study groups (0.94, 0.75 to 1.17; table 2). Dexamethasone was associated with reduced rates of postoperative vomiting and acute kidney injury (0.66, 0.44 to 0.99 and 0.52, 0.30 to 0.91, respectively; table 2). Postoperative C reactive protein blood levels showed a significant decrease in the dexamethasone group compared with placebo group (adjusted estimate -3.37 , 95% confidence interval -5.65 to -1.09). No statistically significant differences were found for the other secondary outcomes (table 2).

Safety was assessed in the intention-to-treat population (table 3, also see supplementary table G for a complete list of severe adverse events). Nine of 613 participants (1.5%) in the dexamethasone group and 12 of 609 (2.0%) in the placebo group received glucocorticoids as rescue treatment. The numbers of participants experiencing adverse events were 288 of 613 (47.0%) in the dexamethasone group and 296 of 609 (48.6%) in the placebo group (odds ratio 0.92, 95% confidence interval 0.74 to 1.15, $P=0.46$). The rates of normal healing, delayed healing, and surgical wound dehiscence did not differ between the two groups ($P=0.79$, $P=0.50$, and $P=0.58$, respectively). In the dexamethasone group, 166 of 613 participants (27.4%) required insulin for hyperglycaemia compared with 131 patients of 609 (21.5%) in the placebo group (odds ratio 1.36, 0.99 to 1.88; $P=0.06$).

Discussion

In this multicentre, double blind, randomised controlled trial of patients undergoing major non-cardiac surgery, dexamethasone administered postoperatively was not associated with a significant reduction in complications and mortality at 14 days after surgery.

Dexamethasone was, however, associated with a significant reduction in the rate of complications and all cause mortality at 14 days after surgery in the a

priori stratum of participants who did not undergo an intrathoracic procedure. In this population, respiratory complications were probably mainly caused by excessive systemic postoperative inflammation, whereas lung complications after intrathoracic procedures probably relate to atelectasis caused by direct tissue damage and are therefore probably less responsive to systemic corticosteroids. The result of the subgroup analysis suggests caution in using dexamethasone in patients after intrathoracic surgery.

Two mechanisms might explain why corticosteroids could decrease the risk of major complications after surgery. Firstly, the potent anti-inflammatory effects of dexamethasone might reduce the excessive postoperative inflammatory response that results in remote organ failure and immune cell apoptosis. In support of this mechanism, we observed a major decrease in C reactive protein blood concentrations in the dexamethasone group compared with placebo group. We decided to administer dexamethasone postoperatively at a time when inflammation had already been initiated, because exogenous corticosteroids are associated with leucocyte apoptosis during homeostasis but are immunostimulant during inflammation.²⁶ Secondly, glucocorticoids might also restore immune functions, which are decreased in patients admitted to hospital at risk of secondary infections.²⁷ When glucocorticoids are administered during a systemic inflammatory response, blood concentrations of anti-inflammatory cytokines decrease, concentrations of interferon γ and interleukin-12 increase, and the phagocytic abilities of neutrophils improves.²⁸⁻³⁰ The use of moderate doses of corticosteroids to reduce the risk of infection is probably counterintuitive. In our study, however, the relative risk for the primary outcome measure in patients treated with dexamethasone was 0.81, which is within the 95% confidence intervals of the estimated effects of glucocorticoids for the treatment or prevention of sepsis.^{10 31} Notably, corticosteroids have been shown to reduce the risk of early death in patients with septic shock.³¹ In acute inflammatory processes, corticosteroids have been shown to reduce the risk of pneumonia after severe trauma⁹ and after traumatic brain injury,¹⁰ and dexamethasone has been shown to decrease the severity of community acquired pneumonia.^{32 33} Respiratory problems are among the most common complications after major surgery,^{4 20} and the present results suggest that dexamethasone could help to reduce the need for mechanical ventilation for respiratory failure postoperatively.

Comparison with other studies

Results from a meta-analysis of the perioperative use of corticosteroids after major abdominal surgery³⁴ comprising 439 patients from 11 randomised controlled trials suggested that corticosteroids could decrease the risk of major complications. In another meta-analysis, comprising 381 patients, however, corticosteroids were not associated with a reduced risk of pulmonary complications after transthoracic

Table 2 | Outcomes in participants assigned to dexamethasone or placebo after major non-cardiac surgery. Values are numbers (percentages) unless stated otherwise

Outcomes	Dexamethasone group (n=595)	Placebo group (n=589)	Estimate (95%CI)	P value
Primary outcome: complications and mortality at 14 days	101 (17.0)	117 (19.9)	0.81 (0.60 to 1.08)*	0.15
All cause mortality	6 (1.0)	7 (1.2)	0.84 (0.52 to 1.38)†	0.5
Postoperative pneumonia or sepsis, or both	78 (13.1)	94 (16.0)	0.82 (0.60 to 1.11)‡	0.2
Mechanical ventilation for respiratory failure	41 (6.9)	52 (8.8)	0.70 (0.53 to 0.93)‡	0.015
Infection localisation:				
Pneumonia	13 (2.1)	18 (3.1)	0.63 (0.31 to 1.31)*	
Surgical site	52 (8.7)	57 (9.7)	1.13 (0.63 to 2.02)*	
Septicaemia	6 (1.0)	11 (1.9)	0.65 (0.23 to 1.85)*	
Urinary tract	14 (2.4)	14 (2.4)	1.32 (0.64 to 2.75)*	
Infection severity:			0.85 (0.45 to 1.61)§	
Sepsis	67 (74.4)	75 (72.8)		
Severe sepsis	17 (18.9)	18 (17.5)		
Septic shock	6 (6.7)	10 (9.7)		
Non-invasive mechanical ventilation:				
Day 14:	33 (5.6)	46 (7.8)	0.67 (0.41 to 1.09)*	
Median (interquartile range) duration (days)	3 (2-5)	6 (2-9)	0.69 (0.51 to 0.94)‡	
Invasive mechanical ventilation:				
Day 14	15 (2.5)	18 (3.1)	0.80 (0.40 to 1.64)*	
Median (interquartile range) duration of mechanical ventilation (days)	2 (0-7)	2 (1-4)	0.76 (0.43 to 1.32)‡	
Clavien-Dindo grade at day 28:			0.94 (0.75 to 1.17)§	
0 (no complications)	340 (57.1)	315 (53.6)		
1 (no intervention)	34 (5.7)	37 (6.3)		
2 (drug intervention)	117 (19.7)	141 (24)		
3a-b (radio-intervention or surgery)	74 (12.4)	63 (10.7)		
4a-b (ICU admission)	19 (3.2)	21 (3.6)		
5 (death)	11 (1.9)	11 (1.9)		
Mean (SD) SOFA score:	n=546	n=541	0.02 (-0.12 to 0.17)¶	
Day 1	0.6 (1.4)	0.6 (1.4)		
Day 3	0.5 (1.3)	0.5 (1.3)		
Day 5	0.5 (1.3)	0.5 (1.3)		
Day 7	0.5 (1.3)	0.5 (1.3)		
Day 9	0.5 (1.3)	0.5 (1.3)		
Day 11	0.5 (1.3)	0.5 (1.3)		
Day 13	0.5 (1.3)	0.5 (1.3)		
Day 15	0.5 (1.3)	0.5 (1.3)		
Day 17	0.5 (1.3)	0.5 (1.3)		
Day 19	0.5 (1.3)	0.5 (1.3)		
Day 21	0.5 (1.3)	0.5 (1.3)		
Day 23	0.5 (1.3)	0.5 (1.3)		
Day 25	0.5 (1.3)	0.5 (1.3)		
Day 27	0.5 (1.3)	0.5 (1.3)		
Day 29	0.5 (1.3)	0.5 (1.3)		
Day 31	0.5 (1.3)	0.5 (1.3)		
Day 33	0.5 (1.3)	0.5 (1.3)		
Day 35	0.5 (1.3)	0.5 (1.3)		
Day 37	0.5 (1.3)	0.5 (1.3)		
Day 39	0.5 (1.3)	0.5 (1.3)		
Day 41	0.5 (1.3)	0.5 (1.3)		
Day 43	0.5 (1.3)	0.5 (1.3)		
Day 45	0.5 (1.3)	0.5 (1.3)		
Day 47	0.5 (1.3)	0.5 (1.3)		
Day 49	0.5 (1.3)	0.5 (1.3)		
Day 51	0.5 (1.3)	0.5 (1.3)		
Day 53	0.5 (1.3)	0.5 (1.3)		
Day 55	0.5 (1.3)	0.5 (1.3)		
Day 57	0.5 (1.3)	0.5 (1.3)		
Day 59	0.5 (1.3)	0.5 (1.3)		
Day 61	0.5 (1.3)	0.5 (1.3)		
Day 63	0.5 (1.3)	0.5 (1.3)		
Day 65	0.5 (1.3)	0.5 (1.3)		
Day 67	0.5 (1.3)	0.5 (1.3)		
Day 69	0.5 (1.3)	0.5 (1.3)		
Day 71	0.5 (1.3)	0.5 (1.3)		
Day 73	0.5 (1.3)	0.5 (1.3)		
Day 75	0.5 (1.3)	0.5 (1.3)		
Day 77	0.5 (1.3)	0.5 (1.3)		
Day 79	0.5 (1.3)	0.5 (1.3)		
Day 81	0.5 (1.3)	0.5 (1.3)		
Day 83	0.5 (1.3)	0.5 (1.3)		
Day 85	0.5 (1.3)	0.5 (1.3)		
Day 87	0.5 (1.3)	0.5 (1.3)		
Day 89	0.5 (1.3)	0.5 (1.3)		
Day 91	0.5 (1.3)	0.5 (1.3)		
Day 93	0.5 (1.3)	0.5 (1.3)		
Day 95	0.5 (1.3)	0.5 (1.3)		
Day 97	0.5 (1.3)	0.5 (1.3)		
Day 99	0.5 (1.3)	0.5 (1.3)		
Day 101	0.5 (1.3)	0.5 (1.3)		
Day 103	0.5 (1.3)	0.5 (1.3)		
Day 105	0.5 (1.3)	0.5 (1.3)		
Day 107	0.5 (1.3)	0.5 (1.3)		
Day 109	0.5 (1.3)	0.5 (1.3)		
Day 111	0.5 (1.3)	0.5 (1.3)		
Day 113	0.5 (1.3)	0.5 (1.3)		
Day 115	0.5 (1.3)	0.5 (1.3)		
Day 117	0.5 (1.3)	0.5 (1.3)		
Day 119	0.5 (1.3)	0.5 (1.3)		
Day 121	0.5 (1.3)	0.5 (1.3)		
Day 123	0.5 (1.3)	0.5 (1.3)		
Day 125	0.5 (1.3)	0.5 (1.3)		
Day 127	0.5 (1.3)	0.5 (1.3)		
Day 129	0.5 (1.3)	0.5 (1.3)		
Day 131	0.5 (1.3)	0.5 (1.3)		
Day 133	0.5 (1.3)	0.5 (1.3)		
Day 135	0.5 (1.3)	0.5 (1.3)		
Day 137	0.5 (1.3)	0.5 (1.3)		
Day 139	0.5 (1.3)	0.5 (1.3)		
Day 141	0.5 (1.3)	0.5 (1.3)		
Day 143	0.5 (1.3)	0.5 (1.3)		
Day 145	0.5 (1.3)	0.5 (1.3)		
Day 147	0.5 (1.3)	0.5 (1.3)		
Day 149	0.5 (1.3)	0.5 (1.3)		
Day 151	0.5 (1.3)	0.5 (1.3)		
Day 153	0.5 (1.3)	0.5 (1.3)		
Day 155	0.5 (1.3)	0.5 (1.3)		
Day 157	0.5 (1.3)	0.5 (1.3)		
Day 159	0.5 (1.3)	0.5 (1.3)		
Day 161	0.5 (1.3)	0.5 (1.3)		
Day 163	0.5 (1.3)	0.5 (1.3)		
Day 165	0.5 (1.3)	0.5 (1.3)		
Day 167	0.5 (1.3)	0.5 (1.3)		
Day 169	0.5 (1.3)	0.5 (1.3)		
Day 171	0.5 (1.3)	0.5 (1.3)		
Day 173	0.5 (1.3)	0.5 (1.3)		
Day 175	0.5 (1.3)	0.5 (1.3)		
Day 177	0.5 (1.3)	0.5 (1.3)		
Day 179	0.5 (1.3)	0.5 (1.3)		
Day 181	0.5 (1.3)	0.5 (1.3)		
Day 183	0.5 (1.3)	0.5 (1.3)		
Day 185	0.5 (1.3)	0.5 (1.3)		
Day 187	0.5 (1.3)	0.5 (1.3)		
Day 189	0.5 (1.3)	0.5 (1.3)		
Day 191	0.5 (1.3)	0.5 (1.3)		
Day 193	0.5 (1.3)	0.5 (1.3)		
Day 195	0.5 (1.3)	0.5 (1.3)		
Day 197	0.5 (1.3)	0.5 (1.3)		
Day 199	0.5 (1.3)	0.5 (1.3)		
Day 201	0.5 (1.3)	0.5 (1.3)		
Day 203	0.5 (1.3)	0.5 (1.3)		
Day 205	0.5 (1.3)	0.5 (1.3)		
Day 207	0.5 (1.3)	0.5 (1.3)		
Day 209	0.5 (1.3)	0.5 (1.3)		
Day 211	0.5 (1.3)	0.5 (1.3)		
Day 213	0.5 (1.3)	0.5 (1.3)		
Day 215	0.5 (1.3)	0.5 (1.3)		
Day 217	0.5 (1.3)	0.5 (1.3)		
Day 219	0.5 (1.3)	0.5 (1.3)		
Day 221	0.5 (1.3)	0.5 (1.3)		
Day 223	0.5 (1.3)	0.5 (1.3)		
Day 225	0.5 (1.3)	0.5 (1.3)		
Day 227	0.5 (1.3)	0.5 (1.3)		
Day 229	0.5 (1.3)	0.5 (1.3)		
Day 231	0.5 (1.3)	0.5 (1.3)		
Day 233	0.5 (1.3)	0.5 (1.3)		
Day 235	0.5 (1.3)	0.5 (1.3)		
Day 237	0.5 (1.3)	0.5 (1.3)		
Day 239	0.5 (1.3)	0.5 (1.3)		
Day 241	0.5 (1.3)	0.5 (1.3)		
Day 243	0.5 (1.3)	0.5 (1.3)		
Day 245	0.5 (1.3)	0.5 (1.3)		
Day 247	0.5 (1.3)	0.5 (1.3)		
Day 249	0.5 (1.3)	0.5 (1.3)		
Day 251	0.5 (1.3)	0.5 (1.3)		
Day 253	0.5 (1.3)	0.5 (1.3)		
Day 255	0.5 (1.3)	0.5 (1.3)		
Day 257	0.5 (1.3)	0.5 (1.3)		
Day 259	0.5 (1.3)	0.5 (1.3)		
Day 261	0.5 (1.3)	0.5 (1.3)		
Day 263	0.5 (1.3)	0.5 (1.3)		
Day 265	0.5 (1.3)	0.5 (1.3)		
Day 267	0.5 (1.3)	0.5 (1.3)		
Day 269	0.5 (1.3)	0.5 (1.3)		
Day 271	0.5 (1.3)	0.5 (1.3)		
Day 273	0.5 (1.3)	0.5 (1.3)		
Day 275	0.5 (1.3)	0.5 (1.3)		
Day 277	0.5 (1.3)	0.5 (1.3)		
Day 279	0.5 (1.3)	0.5 (1.3)		
Day 281	0.5 (1.3)	0.5 (1.3)		
Day 283	0.5 (1.3)	0.5 (1.3)		
Day 285	0.5 (1.3)	0.5 (1.3)		
Day 287	0.5 (1.3)	0.5 (1.3)		
Day 289	0.5 (1.3)	0.5 (1.3)		
Day 291	0.5 (1.3)	0.5 (1.3)		
Day 293	0.5 (1.3)	0.5 (1.3)		
Day 295	0.5 (1.3)	0.5 (1.3)		
Day 297	0.5 (1.3)	0.5 (1.3)		
Day 299	0.5 (1.3)	0.5 (1.3)		
Day 301	0.5 (1.3)	0.5 (1.3)		
Day 303	0.5 (1.3)	0.5 (1.3)		
Day 305	0.5 (1.3)	0.5 (1.3)		
Day 307	0.5 (1.3)	0.5 (1.3)		
Day 309	0.5 (1.3)	0.5 (1.3)		
Day 311	0.5 (1.3)	0.5 (1.3)		
Day 313	0.5 (1.3)	0.5 (1.3)		
Day 315	0.5 (1.3)	0.5 (1.3)		
Day 317	0.5 (1.3)	0.5 (1.3)		
Day 319	0.5 (1.3)	0.5 (1.3)		
Day 321	0.5 (1.3)	0.5 (1.3)		
Day 323	0.5 (1.3)	0.5 (1.3)		
Day 325	0.5 (1.3)	0.5 (1.3)		
Day 327	0.5 (1.3)	0.5 (1.3)		
Day 329	0.5 (1.3)	0.5 (1.3)		
Day 331	0.5 (1.3)	0.5 (1.3)		
Day 333	0.5 (1.3)	0.5 (1.3)		
Day 335	0.5 (1.3)	0.5 (1.3)		
Day 337	0.5 (1.3)	0.5 (1.3)		
Day 339	0.5 (1.3)	0.5 (1.3)		
Day 341	0.5 (1.3)	0.5 (1.3)		
Day 343	0.5 (1.3)	0.5 (1.3)		
Day 345	0.5 (1.3)	0.5 (1.3)		
Day 347	0.5 (1.3)	0.5 (1.3)		
Day 349	0.5 (1.3)	0.5 (1.3)		
Day 351	0.5 (1.3)	0.5 (1.3)		
Day 353	0.5 (1.3)	0.5 (1.3)		
Day 355	0.5 (1.3)	0.5 (1.3)		
Day 357	0.5 (1.3)	0.5 (1.3)		
Day 359	0.5 (1.3)	0.5 (1.3)		
Day 361	0.5 (1.3)	0.5 (1.3)		
Day 363	0.5 (1.3)	0.5 (1.3)		
Day 365	0.5 (1.3)	0.5 (1.3)		
Day 367	0.5 (1.3)	0.5 (1.3)		
Day 369	0.5 (1.3)	0.5 (1.3)		
Day 371	0.5 (1.3)	0.5 (1.3)		
Day 373	0.5 (1.3)	0.5 (1.3)		
Day 375	0.5 (1.3)	0.5 (1.3)		
Day 377	0.5 (1.3)	0.5 (1.3)		
Day 379	0.5 (1.3)	0.5 (1.3)		
Day 381	0.5 (1.3)	0.5 (1.3)		
Day 383	0.5 (1.3)	0.5 (1.3)		
Day 385	0.5 (1.3)	0.5 (1.3)		
Day 387	0.5 (1.3)	0.5 (1.3)		
Day 389	0.5 (1.3)	0.5 (1.3)		
Day 391	0.5 (1.3)	0.5 (1.3)		
Day 393	0.5 (1.3)	0.5 (1.3)		
Day 395	0.5 (1.3)	0.5 (1.3)		
Day 397	0.5 (1.3)	0.5 (1.3)		
Day 399	0.5 (1.3)	0.5 (1.3)		
Day 401	0.5 (1.3)	0.5 (1.3)		
Day 403	0.5 (1.3)	0.5 (1.3)		
Day 405	0.5 (1.3)	0.5 (1.3)		
Day 407	0.5 (1.3)	0.5 (1.3)		
Day 409	0.5 (1.3)	0.5 (1.3)		
Day 411	0.5 (1.3)	0.5 (1.3)		
Day 413	0.5 (1.3)	0.5 (1.3)		
Day 415	0.5 (1.3)	0.5 (1.3)		
Day 417	0.5 (1.3)	0.5 (1.3)		
Day 419	0.5 (1.3)	0.5 (1.3)		
Day 421	0.5 (1.3)	0.5 (1.3)		
Day 423	0.5 (1.3)	0.5 (1.3)		
Day 425	0.5 (1.3)	0.5 (1.3)		
Day 427	0.5 (1.3)	0.5 (1.3)		
Day 429	0.5 (1.3)	0.5 (1.3)		

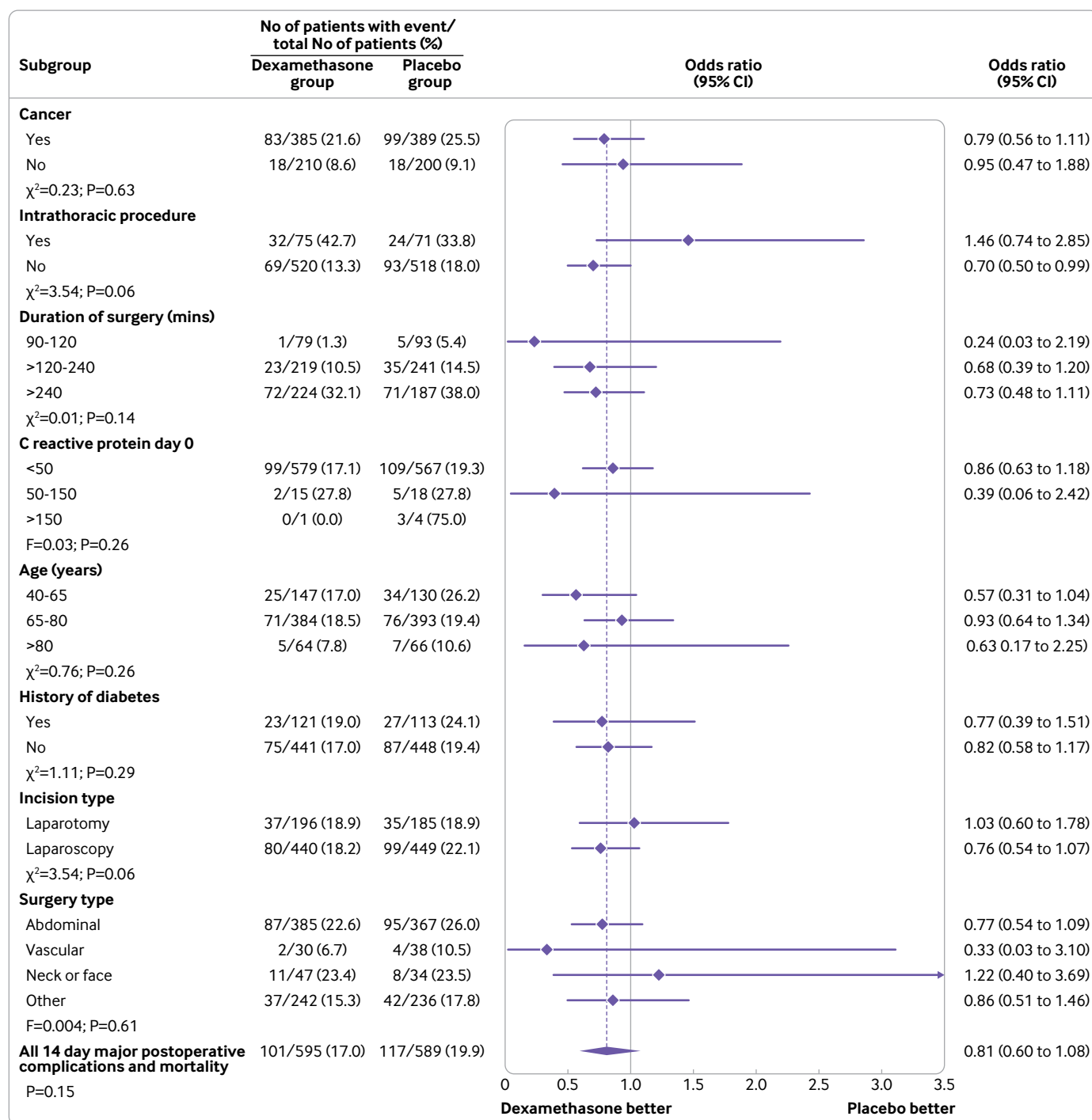


Fig 2 | Subgroup analysis of complications or all cause mortality at 14 days after major non-cardiac surgery. Size of square reflects the relative numbers in each subgroup, and horizontal bars are 95% confidence intervals. It was not possible to analyse the subgroup C reactive protein >150 mg/mL

80% of patients undergoing surgery will receive dexamethasone perioperatively for antiemetic prophylaxis.³⁶ With the exception of hyperglycaemia and transient requirement for insulin, our results show that even at higher doses than the classic antiemetic regimen used in surgery, dexamethasone is well tolerated postoperatively—confirming the results obtained by the Cochrane review group.¹⁵ It has been suggested that perioperative hyperglycaemia

is associated with adverse outcomes in general surgery patients with and without diabetes. The risk of an adverse event, however, has been linked to hyperglycaemia only in patients without diabetes, and this is probably related to the underuse of insulin in these patients.³⁷⁻³⁹ The clinical relevance of the mild and transient hyperglycaemia reported after dexamethasone use is questionable. We observed that a reasonable increase in the dose of insulin within the

Table 3 | Safety outcomes in participants assigned to dexamethasone or placebo after major non-cardiac surgery. Values are numbers (percentages) unless stated otherwise

	Dexamethasone group (n=613)	Placebo group (n=609)	Estimate (95%CI)	P values
Adverse events	288 (47.0)	296 (48.6)	0.92 (0.74 to 1.15)*	0.46
Severe adverse events	106 (17.3)	103 (16.9)	1.03 (0.75 to 1.42)*	0.86
Gastrointestinal adverse events:				
Ulceration	3 (0.5)	2 (0.3)	1.50 (0.26 to 8.69)*	0.65
Bleeding	18 (3.0)	14 (2.3)	1.29 (0.47 to 2.13)*	0.49
Anastomotic leakage	17 (2.8)	23 (3.8)	0.70 (0.38 to 1.31)*	0.27
Metabolic disorders†:				
Hypokalaemia	74 (12.4)	110 (18.8)	0.59 (0.43 to 0.81)*	0.001
Hyponatraemia	164 (27.4)	144 (24.6)	1.14 (0.89 to 1.45)*	0.31
Hypernatraemia	8 (1.3)	20 (3.4)	0.38 (0.17 to 0.86)*	0.02
Hypocalcaemia	159 (29.7)	190 (36.1)	0.71 (0.56 to 0.90)*	0.005
Median (interquartile range) glycaemia (mmol/L):			9.56 (–7.91 to 27.03)‡	0.28
Day 1	8.4 (6.9–10.2)	7.3 (6.3–8.8)		
Day 2	7.7 (6.4–9.2)	7.0 (6.0–8.2)		
Day 3	6.2 (5.2–7.6)	6.4 (5.5–7.8)		
Insulin treatment	166 (27.4)	131 (21.5)	1.36 (0.99 to 1.88)*	0.06
Median (interquartile range) total dose of insulin (IU/day):			–0.97 (–5.73 to 3.78)‡	0.69
Day 1	27.0 (12.0–46.0)	24.0 (11.0–44.0)		
Day 2	24.0 (12.0–42.0)	24.0 (9.0–38.0)		
Day 3	16.0 (3.0–30.5)	15.5 (4.0–37.5)		
Healing:				
Normal	541 (89.6)	536 (89.9)	1.05 (0.72 to 1.54)*	0.79
Delayed	41 (6.8)	34 (5.7)	1.22 (0.64 to 2.33)*	0.50
Wound dehiscence	22 (3.6)	26 (4.4)	0.84 (0.46 to 1.55)*	0.58

*Marginal odds ratio calculated with logistic regression model adjusted on stratification factors and centres as random effect.

†According to on-site local normal values.

‡Marginal estimates calculated with mixed linear regression adjusted on stratification factors and centres as random effect.

first 48 hours enabled normalisation of the glycaemia. We did not find an association between a history of diabetes and the effect of dexamethasone on the primary outcome. In accordance with our data, it has been shown recently that high doses of dexamethasone administered perioperatively to children after cardiac surgery was not associated with major harm.⁴⁰

Strengths and limitations of this study

The strengths of this double blind, randomised controlled trial include its large size and the number of participating sites. To reduce variability in the perioperative care of patients, the clinicians were asked to follow local recommendations for antimicrobial prophylaxis, protective ventilation (low tidal volume ventilation), prevention of hypotension, and duration of sedation. We evaluated a wide variety of surgical interventions and therefore our results should be considered as highly representative of daily practice. Our study did, however, have some limitations. Firstly, the study dose of dexamethasone was higher than that recommended for the prevention of nausea and vomiting. Interestingly, the range of dexamethasone in equivalent hydrocortisone was 200–400 mg/day, which is close to the dose administered in the ICU for septic shock or trauma.⁴¹ Our results do, however, suggest that dexamethasone should be used with caution in patients undergoing intrathoracic procedures; a further limitation is the lack of patient and public involvement. Secondly, we used a composite primary outcome, which cannot show a reduction in each specific postoperative complication; our score has

not been previously validated and did not include postoperative cardiac complications. Also, the primary outcome was evaluated within 14 days of surgery and a slightly longer period could have been chosen. Thirdly, the modified intention-to-treat analysis, which only included participants who had received at least one dose of treatment, was chosen as the primary analysis because we aimed to evaluate for the first time a new dose of dexamethasone administered postoperatively to treat complications related to the inflammatory response; however, as inflammation commences at the time of tissue injury from skin incision, an invaluable approach might have been to administer dexamethasone earlier. Fourthly, participants were randomised in a fixed block size, whereas the use of random permuted block size could have helped to reduce the risk of selection bias. Moreover, the randomisation was not stratified on centres, which could theoretically affect the overall balance of the treatment groups. Yet, the treatment effects varied little across the centres. Finally, the study power was perhaps too small to show an effect of dexamethasone on the primary outcome. We aimed to reduce postoperative inflammation using dexamethasone and hypothesised that the treatment effect would be consistent across a wide range of prolonged surgery. The subgroup analyses, however, suggested that the heterogeneity of the surgery and patients had probably contributed to an imprecise estimation of the treatment effect, reducing the study power. The effect size used for the power calculation was based on high risk patients but could have been overestimated. With

a 19.9% rate in the control group and 17.0% in the dexamethasone group, a total of 5616 patients would have been needed to detect this difference between the two groups with a 5% type I error and a power of 80% in a two sided test.

Conclusion

Postoperative treatment with dexamethasone was not associated with a significant reduction in the incidence of complications and death in patients undergoing major non-cardiac surgery. The 95% confidence interval for the main result was, however, wide and therefore suggests the possibility of important clinical effectiveness. At present, the use of glucocorticoids to prevent postoperative systemic complications is not widely adopted. Our trial described an innovative regimen adapted to a patient's body weight that was well tolerated postoperatively.

AUTHOR AFFILIATIONS

¹CHU Nantes, Université de Nantes, Pôle Anesthésie-Réanimation, Service d'Anesthésie Réanimation Chirurgicale, Hôtel Dieu, Nantes, France

²Service d'Anesthésie, Centre Hospitalier Le Mans, Le Mans, France

³Centre Hospitalier Universitaire (CHU) Lille, Pôle Anesthésie Réanimation, Lille, France

⁴Service d'Anesthésie, Hôpital Privé du Confluent, Nantes, France

⁵CHU de Poitiers, Université de Poitiers, Service d'Anesthésie-Réanimation, Poitiers, France

⁶Hôpital Saint Antoine, Service d'Anesthésie Réanimation Chirurgicale, Assistance publique des hôpitaux de Paris, Paris, France

⁷Institut Paoli Calmette, Service d'Anesthésie, Marseille, France

⁸Anesthesia and Critical Care Department B, Saint Eloi Teaching Hospital, PhyMedExp, Centre Hospitalier Universitaire Montpellier, University of Montpellier, INSERM U1046, CNRS UMR 9214, Montpellier, France

⁹Service d'Anesthésie et Réanimation, Hôpital Estaing, CHU Clermont Ferrand, Clermont-Ferrand, France

¹⁰Department of Anesthesiology and Critical Care Medicine, Hôpital Nord, Aix Marseille University, Assistance Publique Hôpitaux de Marseille, Marseille, France

¹¹Département d'Anesthésie & VVC, Gustave Roussy Cancer Center, Villejuif, France

¹²Service d'Anesthésie Réanimation, Groupe Hospitalier Sud, Civils de Lyon, Pierre Benite, France

¹³CHU Nantes, Université de Nantes, Pôle Anesthésie-Réanimation, Service d'Anesthésie Réanimation Chirurgicale, Hôpital Guillaume et René Laennec, Saint-Herblain, France

¹⁴CH Valenciennes, Service d'Anesthésie, Valenciennes, France

¹⁵CHU de Nantes, Direction de la Recherche, Plateforme de Méthodologie et Biostatistique, Nantes, France

¹⁶CHU Nantes, Service Pharmacie, Hôtel Dieu, Nantes, France

¹⁷Université de Nantes, Université de Tours, INSERM, SPHERE U1246, Nantes, France

We thank the families and participants who took part in the study as well as the clinical and research staff at the trial sites.

PACMAN study group: Mathieu Oudot, hospital practitioner, Service d'Anesthésie, Centre Hospitalier Départemental Vendée, La Roche Sur Yon, France; Thomas Rimmelé, professor in anaesthesia and critical care medicine, Hôpital Edouard Herriot, Hospice Civils de Lyon Lyon, France; Serge Molliex, professor in anaesthesia and critical care medicine, CHU de Saint Etienne, Service d'Anesthésie-Réanimation, Saint Etienne, France; Olivier Huet, professor in anaesthesia and critical care medicine, CHU de Brest, Université de Brest, Service d'Anesthésie-Réanimation, Brest, France; Vincent Minville, professor in anaesthesia and critical care medicine, CHU Toulouse, Hôpital Purpan, Service d'Anesthésie-Réanimation, Toulouse, France; Bertrand

Dureil, professor in anaesthesia and critical care medicine, CHU Rouen, Service d'Anesthésie-Réanimation, Rouen, France; Florian Capron, private hospital practitioner, Clinique Jules Verne, Service d'anesthésie, Nantes, France; Benoit Plaud, professor in anaesthesia and critical care medicine, Assistance Publique Hôpitaux de Paris, Hôpital Saint Louis, Paris, France; Sigismond Lasocki, professor in anaesthesia and critical care medicine, CHU d'Angers, Service d'Anesthésie-Réanimation, Angers, France; Pascale Le Maguet, hospital practitioner, CH de Quimper, Service d'Anesthésie, Quimper, France; and Hélène Beloeil, professor in anaesthesia and critical care medicine, CHU Rennes, Service d'Anesthésie-Réanimation, Rennes, France.

Data and safety monitoring boards: Djillali Annane (Hôpital Raymond-Poincaré, AP/HP, France), Elie Azoulay (Hôpital Saint Louis, AP/HP, France), Jérémie Lefevre (Hôpital Saint Antoine, AP/HP, France), Emilie Vierrion (Université de Nantes, France) and Jean Louis Vincent (Hôpital Erasme, Brussels, Belgium).

Contributors: KA obtained funding from the French Ministry of Health to undertake the study. He is the guarantor and accepts full responsibility for the work. KA and AR conceived, designed, and supervised the study, interpreted the data, and wrote the report. MP and FF performed the statistical analyses. MP was responsible for data management and statistical analysis. All of the authors participated in data collection and acquisition; reviewed the manuscript for important intellectual content; and gave administrative, technical, or material support. Additional contributors were Celine Lerebourg and Delphine Flattres Duchaussoy (research technicians), June Fortin, and Anne Omnes (administrative support, Direction de la recherche clinique Nantes). The lead author had full access to all the data in the study and takes responsibility for the integrity, transparency of the data, and the accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: This study was funded by the French Ministry of Health (PHRCN 2016, RC16_0442). Nantes University Hospital sponsored the study. The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. There was no agreement concerning confidentiality of the data between the sponsor and the authors. Mylan (which supplied dexamethasone) did not have any role in the conduct of the trial or participate in the analysis, interpretation, or writing and review of the manuscript.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from the French Ministry of Health and Nantes University Hospital for the submitted work; KA reports receiving lecture fees from Baxter, Fisher and Paykel, and LFB and consulting fees from Edward Lifesciences, LFB (Laboratoire français du fractionnement et des biotechnologies). MB reports receiving consulting fees from Becton Dickinson. SJ reports receiving personal fees from Drager, Medtronic, Baxter, Medtronic, Fisher & Paykel, and Fresenius-Xenios. ML reports receiving consulting fees from Aspen, Orion, MSD, Pfizer, 3M, Octapharma, and Edwards Lifesciences. EF reports receiving consulting fees from Drager Medical, GE Healthcare, Edwards Lifesciences, and Orion Pharma, and lectures fees from Fresenius Kabi, Baxter, and Fisher & Paykel. AR reports receiving consulting fees from Merck and bioMérieux.

Ethical approval: This trial was approved by Sud Méditerranée V institutional review board in June 2017. The trial was conducted in accordance with the declaration of Helsinki.

Data sharing: Deidentified data about the individual participants will be shared with researchers of further studies. Request for data sharing will be handled in line with the data access and sharing policy of Nantes University Hospital.

The lead author (KA) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Participating institutions and anaesthesiology and surgical departments were informed of the results. Results also can be communicated to study participants who express an interest during clinic visits. The results were presented at the French Society of Anaesthesiology and Critical Care Medicine (<http://www.sfar-lecongres.com/images/Programme-SFAR-2020.pdf>). The main results of the current research will be disseminated to related patients and the public through blogs, press releases, newspapers, and broadcasts.

Provenance and peer review: Not commissioned; externally peer reviewed.

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

- 1 Weiser TG, Haynes AB, Molina G, et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. *Lancet* 2015;385(Suppl 2):S11. doi:10.1016/S0140-6736(15)60806-6
- 2 Bainbridge D, Martin J, Arango M, Cheng D, Evidence-based Peri-operative Clinical Outcomes Research (EPICOR) Group. Perioperative and anaesthetic-related mortality in developed and developing countries: a systematic review and meta-analysis. *Lancet* 2012;380:1075-81. doi:10.1016/S0140-6736(12)60990-8
- 3 Peden CJ, Stephens T, Martin G, et al, Enhanced Peri-Operative Care for High-risk patients (EPOCH) trial group. Effectiveness of a national quality improvement programme to improve survival after emergency abdominal surgery (EPOCH): a stepped-wedge cluster-randomised trial. *Lancet* 2019;393:2213-21. doi:10.1016/S0140-6736(18)32521-2
- 4 Pearse RM, Harrison DA, MacDonald N, et al, OPTIMISE Study Group. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. *JAMA* 2014;311:2181-90. doi:10.1001/jama.2014.5305
- 5 Pearse RM, Moreno RP, Bauer P, et al, European Surgical Outcomes Study (EuSOS) group for the Trials groups of the European Society of Intensive Care Medicine and the European Society of Anaesthesiology. Mortality after surgery in Europe: a 7 day cohort study. *Lancet* 2012;380:1059-65. doi:10.1016/S0140-6736(12)61148-9
- 6 van Berge Henegouwen MJ, van der Poll T, van Deventer SJ, Gouma DJ. Peritoneal cytokine release after elective gastrointestinal surgery and postoperative complications. *Am J Surg* 1998;175:311-6. doi:10.1016/S0002-9610(98)00010-5
- 7 Lin E, Calvano SE, Lowry SF. Inflammatory cytokines and cell response in surgery. *Surgery* 2000;127:117-26. doi:10.1067/msy.2000.101584
- 8 Annane D, Renault A, Brun-Buisson C, et al, CRICS-TRIGGERSEPP Network. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. *N Engl J Med* 2018;378:809-18. doi:10.1056/NEJMoa1705716
- 9 Roquilly A, Mahe PJ, Seguin P, et al. Hydrocortisone therapy for patients with multiple trauma: the randomized controlled HYPOLYTE study. *JAMA* 2011;305:1201-9. doi:10.1001/jama.2011.360
- 10 Asehnoune K, Seguin P, Allary J, et al, Corti-TC Study Group. Hydrocortisone and fludrocortisone for prevention of hospital-acquired pneumonia in patients with severe traumatic brain injury (Corti-TC): a double-blind, multicentre phase 3, randomised placebo-controlled trial. *Lancet Respir Med* 2014;2:706-16. doi:10.1016/S2213-2600(14)70144-4
- 11 Whitlock RP, Devereaux PJ, Teoh KH, et al, SIRS Investigators. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. *Lancet* 2015;386:1243-53. doi:10.1016/S0140-6736(15)00273-1
- 12 Yared J-P, Bakri MH, Erzurum SC, et al. Effect of dexamethasone on atrial fibrillation after cardiac surgery: prospective, randomized, double-blind, placebo-controlled trial. *J Cardiothorac Vasc Anesth* 2007;21:68-75. doi:10.1053/j.jvca.2005.10.014
- 13 Dieleman JM, Nierich AP, Rosseel PM, et al, Dexamethasone for Cardiac Surgery (DECS) Study Group. Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. *JAMA* 2012;308:1761-7. doi:10.1001/jama.2012.14144
- 14 DREAMS Trial Collaborators and West Midlands Research Collaborative. Dexamethasone versus standard treatment for postoperative nausea and vomiting in gastrointestinal surgery: randomised controlled trial (DREAMS Trial). *BMJ* 2017;357:j1455.
- 15 Polderman JA, Farhang-Razi V, Van Dieren S, et al. Adverse side effects of dexamethasone in surgical patients. *Cochrane Database Syst Rev* 2018;8:CD011940.
- 16 Toner AJ, Ganeshanathan V, Chan MT, Ho KM, Corcoran TB. Safety of Perioperative Glucocorticoids in Elective Noncardiac Surgery: A Systematic Review and Meta-analysis. *Anesthesiology* 2017;126:234-48. doi:10.1097/ALN.0000000000001466
- 17 Asehnoune K, Futier E, Feuillet F, Roquilly A, PACMAN group. PACMAN trial protocol, Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac major surgery: a randomised, multicentre, double-blind, superiority study. *BMJ Open* 2019;9:e021262. doi:10.1136/bmjopen-2017-021262
- 18 Smetana GW, Lawrence VA, Cornell JE, American College of Physicians. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. *Ann Intern Med* 2006;144:581-95. doi:10.7326/0003-4819-144-8-200604180-00009
- 19 Weber WP, Mujagic E, Zwahlen M, et al. Timing of surgical antimicrobial prophylaxis: a phase 3 randomised controlled trial. *Lancet Infect Dis* 2017;17:605-14. doi:10.1016/S1473-3099(17)30176-7
- 20 Futier E, Constantin J-M, Paugam-Burtz C, et al, IMPROVE Study Group. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med* 2013;369:428-37. doi:10.1056/NEJMoa1301082
- 21 Futier E, Lefrant J-Y, Guinot P-G, et al, INPRESS Study Group. Effect of Individualized vs Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery: A Randomized Clinical Trial. *JAMA* 2017;318:1346-57. doi:10.1001/jama.2017.14172
- 22 Chanques G, Conseil M, Roger C, et al, SOS-Ventilation study investigators. Immediate interruption of sedation compared with usual sedation care in critically ill postoperative patients (SOS-Ventilation): a randomised, parallel-group clinical trial. *Lancet Respir Med* 2017;5:795-805. doi:10.1016/S2213-2600(17)30304-1
- 23 Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:801-10. doi:10.1001/jama.2016.0287
- 24 Jaber S, Lescot T, Futier E, et al, NIVAS Study Group. Effect of Noninvasive Ventilation on Tracheal Reintubation Among Patients With Hypoxemic Respiratory Failure Following Abdominal Surgery: A Randomized Clinical Trial. *JAMA* 2016;315:1345-53. doi:10.1001/jama.2016.2706
- 25 Polderman JAW, Farhang-Razi V, van Dieren S, et al. Adverse side-effects of dexamethasone in surgical patients - an abridged Cochrane systematic review. *Anaesthesia* 2019;74:929-39. doi:10.1111/anae.14610
- 26 Lepelletier Y, Zollinger R, Ghirelli C, et al. Toll-like receptor control of glucocorticoid-induced apoptosis in human plasmacytoid dendritic cells (pDCs). *Blood* 2010;116:3389-97. doi:10.1182/blood-2010-05-282913
- 27 Bouras M, Asehnoune K, Roquilly A. Contribution of Dendritic Cell Responses to Sepsis-Induced Immunosuppression and to Susceptibility to Secondary Pneumonia. *Front Immunol* 2018;9:2590. doi:10.3389/fimmu.2018.02590
- 28 Keh D, Boehnke T, Weber-Cartens S, et al. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med* 2003;167:512-20. doi:10.1164/rccm.200205-446OC
- 29 Roquilly A, Broquet A, Jacqueline C, et al. Hydrocortisone prevents immunosuppression by interleukin-10+ natural killer cells after trauma-hemorrhage. *Crit Care Med* 2014;42:e752-61. doi:10.1097/CCM.0000000000000658
- 30 Kaufmann I, Briegel J, Schliephake F, et al. Stress doses of hydrocortisone in septic shock: beneficial effects on opsonization-dependent neutrophil functions. *Intensive Care Med* 2008;34:344-9. doi:10.1007/s00134-007-0868-8
- 31 Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for treating sepsis in children and adults. *Cochrane Database Syst Rev* 2019;12:CD002243. doi:10.1002/14651858.CD002243.pub4
- 32 Meijvis SC, Hardeman H, Remmelts HH, et al. Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011;377:2023-30. doi:10.1016/S0140-6736(11)60607-7
- 33 Horby P, Lim WS, Emberson JR, et al, RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021;384:693-704. doi:10.1056/NEJMoa2021436
- 34 Srinivasa S, Kahokehr AA, Yu T-C, Hill AG. Preoperative glucocorticoid use in major abdominal surgery: systematic review and meta-analysis of randomized trials. *Ann Surg* 2011;254:183-91. doi:10.1097/SLA.0b013e3182261118
- 35 Weijs TJ, Dieleman JM, Ruurda JP, Kroese AC, Knape HJTA, van Hillegersberg R. The effect of perioperative administration of glucocorticoids on pulmonary complications after transthoracic oesophagectomy: a systematic review and meta-analysis. *Eur J Anaesthesiol* 2014;31:685-94. doi:10.1097/EJA.0000000000000093
- 36 Corcoran TB, Edwards T. A survey of antiemetic dexamethasone administration-frequency of use and perceptions of benefits and risks. *Anaesth Intensive Care* 2015;43:167-74. doi:10.1177/0310057X1504300205

- 37 Gandhi GY, Nuttall GA, Abel MD, et al. Intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients. *Mayo Clin Proc* 2005;80:862-6. doi:10.4065/80.7.862
- 38 Coursin DB, Connery LE, Ketzler JT. Perioperative diabetic and hyperglycemic management issues. *Crit Care Med* 2004;32(Suppl):S116-25. doi:10.1097/01.CCM.0000115623.52021.CO
- 39 Frisch A, Chandra P, Smiley D, et al. Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. *Diabetes Care* 2010;33:1783-8. doi:10.2337/dc10-0304
- 40 Lomivorotov V, Kornilov I, Boboshko V, et al. Effect of Intraoperative Dexamethasone on Major Complications and Mortality Among Infants Undergoing Cardiac Surgery: The DECISION Randomized Clinical Trial. *JAMA* 2020;323:2485-92. doi:10.1001/jama.2020.8133
- 41 Pastores SM, Annane D, Rochwerf B. Corticosteroid Guideline Task Force of SCCM and ESICM. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part II): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Intensive Care Med* 2018;44:474-7. doi:10.1007/s00134-017-4951-5

Web appendix: Supplementary materials