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

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.

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

---

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]

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 complications[18] 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 procedure[22] 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

1277
Assessed for eligibility

55
Not randomised
17 Did not meet inclusion criteria
1 Withdrew consent
4 End of inclusion period
37 Other reasons

1222
Underwent randomisation

613
Assigned to dexamethasone
601 Received assigned treatment
12 Did not receive assigned treatment
6 Perioperative injection of dexamethasone outside of protocol
6 Did not receive injection (1 no medical justification, 5 early termination of surgery)

609
Assigned to placebo
593 Received assigned treatment
16 Did not receive assigned treatment
2 Did not meet inclusion criteria
3 Surgery cancelled
7 Perioperative injection of dexamethasone outside of protocol
4 Did not receive injection (1 no medical justification, 3 early termination of surgery)

10
Did not complete follow-up
9 Deaths
1 Major protocol dropout
19
Did not receive second injection

12
Did not complete follow-up
10 Deaths
1 Withdrew consent
1 Major protocol dropout
28
Did not receive second injection

Modified intention to treat (n=1184)

595
Modified intention to treat
18 Excluded
17 Did not receive an injection
1 Refused use of their data

589
Modified intention to treat
20 Excluded
2 Did not meet inclusion criteria
16 Did not receive an injection
2 Refused use of their data

Per protocol (n=1052)

530
Per protocol
65 Excluded
37 Surgery <75 minutes
28 Did not receive two study injections

522
Per protocol
67 Excluded
2 Missing data for primary outcome
30 Surgery <75 minutes
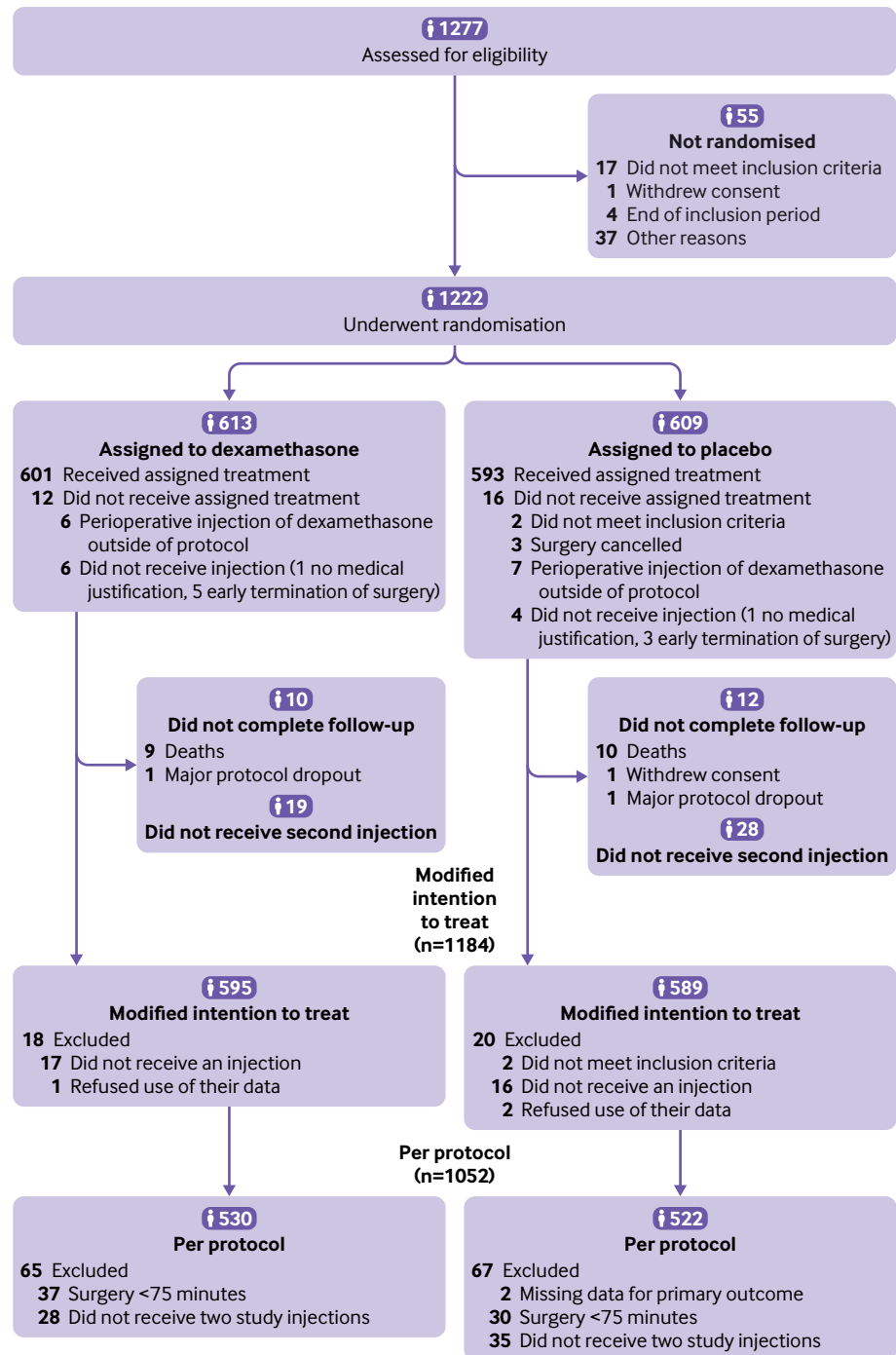**35** Did not receive two study injections

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 (×10^9/L)	7.9 (5.6-8.5)	7.9 (5.6-8.6)	7.4 (5.6-8.3)
Neutrophils (×10^9/L)	4.3 (3.2-5.5)	4.3 (3.2-5.7)	4.3 (5.2-5.3)
Lymphocytes (×10^9/L)	1.7 (1.3-2.2)	1.7 (1.2-2.3)	1.7 (1.3-2.1)
Creatinine (µmol/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 homoeostasis 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 trauma[9] 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 surgery[34] 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)		
	n=511	n=511		
Day 3	0.5 (1.3)	0.5 (1.3)		
	n=595	n=589		
Acute respiratory distress syndrome	11 (1.9)	14 (2.4)	0.78 (0.42 to 1.45)*	
Postoperative acute kidney injury (KDIGO ≥2)	17 (2.9)	33 (5.6)	0.52 (0.30 to 0.91)*	
Median (interquartile range) blood C reactive protein (mg/mL):			−3.37 (−5.65 to −1.09)¶	
Day 0 (before 1st injection)	4 (2 to 7)	4 (1 to 7)		
Day 1	54 (26-98)	82 (46-129)		
Day 2	53 (25-97)	133 (85-206)		
Vomiting	51 (8.6)	73 (12.4)	0.66 (0.44 to 0.99)*	
ICU admission:				
Total	298 (50.1)	290 (49.3)	1.06 (0.82 to 1.36)*	
Scheduled	276 (93.2)	265 (92.3)	1.11 (0.59 to 2.10)*	
Emergency	31 (10.5)	27 (9.4)	1.12 (0.64 to 1.95)*	
Unplanned or readmission	36 (12.1)	34 (11.7)	1.05 (0.64 to 1.74)*	
Median (interquartile range) duration of ICU stay (days)	0 (0-4)	0 (0-5)	1.03 (0.89 to 1.19)‡	
Median (interquartile range) duration of hospital stay (days)	27 (20-28)	27 (21-28)	1.03 (0.92 to 1.14)‡	
Postoperative morbidity at day 7:				
Acute kidney injury (KDIGO 2-3)	4 (0.7)	10 (1.7)	0.39 (0.12 to 1.23)*	
Acute coronary syndrome	1 (0.2)	0 (0.0)	/	
Infection	58 (9.8)	68 (11.5)	0.83 (0.56 to 1.23)*	
Pneumonia	11 (1.9)	16 (2.7)	0.66 (0.31 to 1.44)*	
Surgical site infection	34 (5.7)	34 (5.8)	0.99 (0.59 to 1.67)*	
Sepsis	58 (5.8)	68 (11.5)	0.83 (0.56 to 1.23)*	
Septic shock	2 (0.3)	6 (1.0)		

ICU=intensive care unit; SOFA=sepsis related organ failure assessment score; KDIGO=Kidney Disease: Improving Global Outcomes.
*Marginal odds ratio calculated with logistic regression model adjusted on stratification factors and centres as random effect.
†Marginal hazard ratio calculated with cox model adjusted on stratification factors and centres as random effect.
‡Marginal hazard ratio calculated with competitive risk survival model adjusted on stratification factors and centres as random effect.
§Marginal odds ratio calculated with ordinal logistic regression model adjusted on stratification factors and centres as random effect.
¶Marginal estimate calculated with mixed linear regression adjusted on stratification factors and centres as random effect.

oesophagectomy.[35] In both meta-analyses,[34 35] use of corticosteroids was not associated with adverse effects compared with placebo, and the authors suggested the need for larger population samples in future randomised controlled trials.

Concerns about the potential side effects of dexamethasone have emerged—notably, the risk of postoperative anastomotic leakage, delayed healing, and metabolic disorders such as hyperglycaemia.[16 25] These concerns are important because 30% to
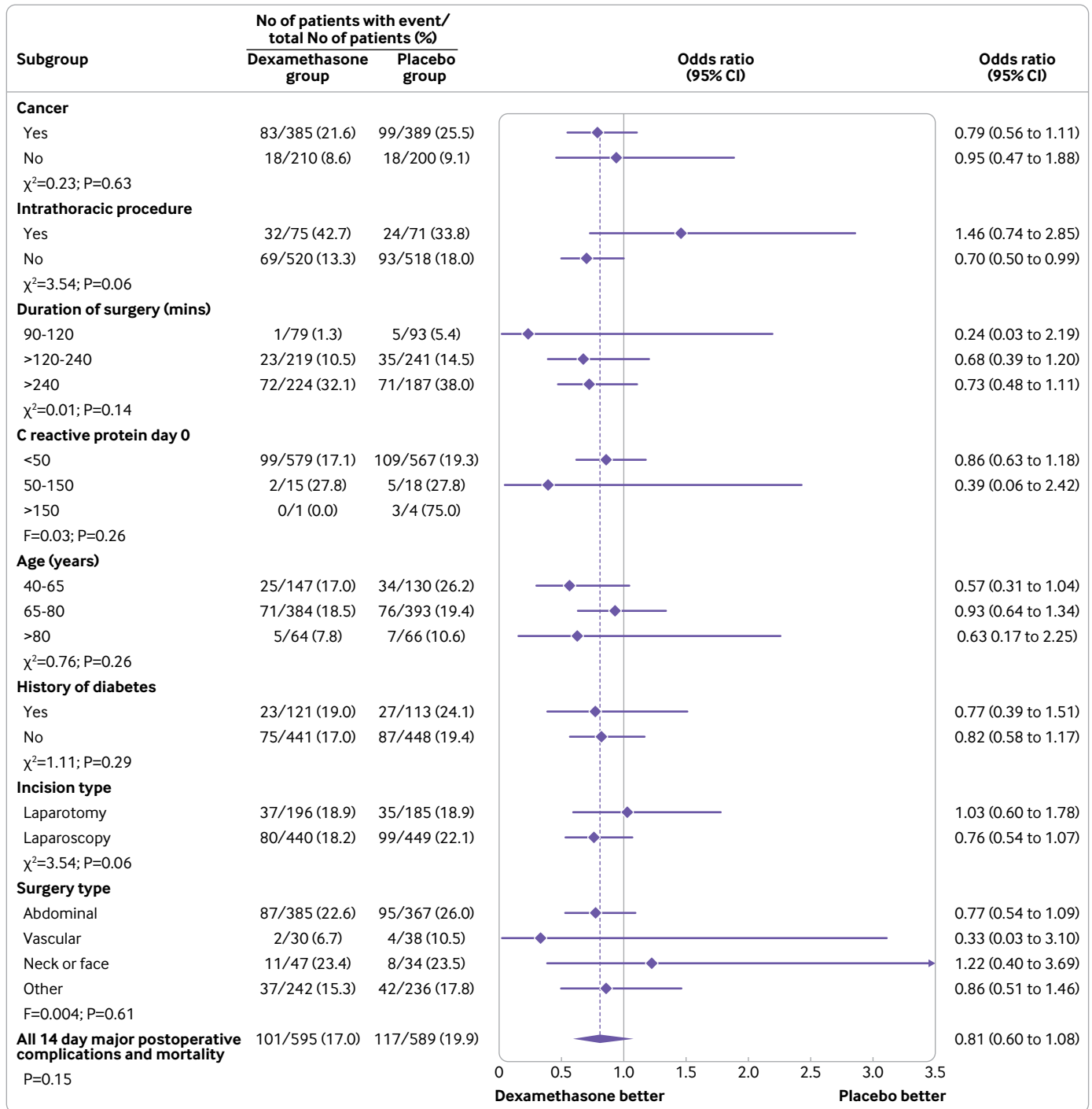
Subgroup	No of patients with event/ total No of patients (%)		Odds ratio (95% CI)	Odds ratio (95% CI)
	Dexamethasone group	Placebo group		
Cancer				
Yes	83/385 (21.6)	99/389 (25.5)		0.79 (0.56 to 1.11)
No	18/210 (8.6)	18/200 (9.1)		0.95 (0.47 to 1.88)
χ^2=0.23; P=0.63				
Intrathoracic procedure				
Yes	32/75 (42.7)	24/71 (33.8)		1.46 (0.74 to 2.85)
No	69/520 (13.3)	93/518 (18.0)		0.70 (0.50 to 0.99)
χ^2=3.54; P=0.06				
Duration of surgery (mins)				
90-120	1/79 (1.3)	5/93 (5.4)		0.24 (0.03 to 2.19)
>120-240	23/219 (10.5)	35/241 (14.5)		0.68 (0.39 to 1.20)
>240	72/224 (32.1)	71/187 (38.0)		0.73 (0.48 to 1.11)
χ^2=0.01; P=0.14				
C reactive protein day 0				
<50	99/579 (17.1)	109/567 (19.3)		0.86 (0.63 to 1.18)
50-150	2/15 (27.8)	5/18 (27.8)		0.39 (0.06 to 2.42)
>150	0/1 (0.0)	3/4 (75.0)		
F=0.03; P=0.26				
Age (years)				
40-65	25/147 (17.0)	34/130 (26.2)		0.57 (0.31 to 1.04)
65-80	71/384 (18.5)	76/393 (19.4)		0.93 (0.64 to 1.34)
>80	5/64 (7.8)	7/66 (10.6)		0.63 0.17 to 2.25)
χ^2=0.76; P=0.26				
History of diabetes				
Yes	23/121 (19.0)	27/113 (24.1)		0.77 (0.39 to 1.51)
No	75/441 (17.0)	87/448 (19.4)		0.82 (0.58 to 1.17)
χ^2=1.11; P=0.29				
Incision type				
Laparotomy	37/196 (18.9)	35/185 (18.9)		1.03 (0.60 to 1.78)
Laparoscopy	80/440 (18.2)	99/449 (22.1)		0.76 (0.54 to 1.07)
χ^2=3.54; P=0.06				
Surgery type				
Abdominal	87/385 (22.6)	95/367 (26.0)		0.77 (0.54 to 1.09)
Vascular	2/30 (6.7)	4/38 (10.5)		0.33 (0.03 to 3.10)
Neck or face	11/47 (23.4)	8/34 (23.5)		1.22 (0.40 to 3.69)
Other	37/242 (15.3)	42/236 (17.8)		0.86 (0.51 to 1.46)
F=0.004; P=0.61				
All 14 day major postoperative complications and mortality	101/595 (17.0)	117/589 (19.9)		0.81 (0.60 to 1.08)
P=0.15				

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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 MI, 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-TRIGGERSEP 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 predendritic 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.C0

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, Rochwerg 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