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Dexamethasone, light anaesthesia, and tight glucose control (DeLiT) randomized controlled trial†

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Editor's key points

- The inflammatory response to surgery may be an important part of the pathophysiology of adverse outcomes after surgery.
- Dexamethasone, tight glycaemic control, and light anaesthesia may attenuate these inflammatory responses.
- This study used a three-way factorial design to test the influence of these interventions on outcome.
- None of the interventions were found to reduce mortality or major morbidity.

Background. The inflammatory response to surgical tissue injury is associated with perioperative morbidity and mortality. We tested the primary hypotheses that major perioperative morbidity is reduced by three potential anti-inflammatory interventions: (i) low-dose dexamethasone, (ii) intensive intraoperative glucose control, and (iii) lighter anaesthesia.

Methods. We enrolled patients having major non-cardiac surgery who were ≥40 yr old and had an ASA physical status ≤IV. In a three-way factorial design, patients were randomized to perioperative i.v. dexamethasone (a total of 14 mg tapered over 3 days) *vs* placebo, intensive *vs* conventional glucose control 80–110 *vs* 180–200 mg dl^{-1}, and lighter *vs* deeper anaesthesia (bispectral index target of 55 *vs* 35). The primary outcome was a collapsed composite of 15 major complications and 30 day mortality. Plasma high-sensitivity (hs) C-reactive protein (CRP) concentration was measured before operation and on the first and second postoperative days.

Results. The overall incidence of the primary outcome was about 20%. The trial was stopped after the second interim analysis with 381 patients, at which all three interventions crossed the futility boundary for the primary outcome. No three-way ($P=0.70$) or two-way (all $P>0.52$) interactions among the interventions were found. There was a significantly smaller increase in hsCRP in patients given dexamethasone than placebo [maximum 108 (64) *vs* 155 (69) mg $litre^{-1}$, $P<0.001$], but none of the other two interventions differentially influenced the hsCRP response to surgery.

Conclusions. Among our three interventions, dexamethasone alone reduced inflammation. However, no intervention reduced the risk of major morbidity or 1 yr mortality.

Trial Registration Identifier. NCT00433251 at www.clinicaltrials.gov.

Keywords: depth of anaesthesia; glucose control; hsCRP; perioperative inflammation; steroid

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The perioperative period is characterized by an intense physiological stress response to surgical trauma.[1] Inflammation is a major component of the surgical stress response.[2]

Inflammation, as measured by C-reactive protein (CRP), is associated with morbidity and mortality in non-surgical settings[3] and in the perioperative period.[4] Salo[5] suggested that blunting the immune response to surgical trauma and associated massive release of inflammatory mediators might reduce perioperative morbidity and mortality.

Steroid administration improves outcomes after cardiac surgery.[6 7] In non-cardiac surgery, steroids have been shown in small trials to improve postoperative fatigue, pain, nausea and vomiting, and to shorten convalescence duration.[8 9] However, the effect of steroids on serious outcomes remains unclear.

Blood glucose concentration is independently related to CRP concentration.[10 11] Treatment of hyperglycaemia yielded contradicting results.[12–15] The effects of

† This article is accompanied by Editorial I.

intraoperative intensive *vs* conventional glucose control on perioperative outcomes in major non-cardiac surgery remain unknown.

Another factor influencing the surgical stress response and inflammation, and thus postoperative outcomes, is anaesthetic management.[16] For example, deep anaesthesia may be associated with adverse outcomes including mortality. Lindholm and colleagues[17] showed that duration at deep anaesthetic levels [bispectral index (BIS)<45] was significantly related to 1 and 2 yr mortality, and that non-survivors spent more time at deep BIS levels than the survivors (hazard ratio of 1.13 h^{-1}). In a cohort of adults having non-cardiac surgery under general anaesthesia, lower BIS levels were independently associated with higher mortality.[18] In this study,[18] as in the Lindholm and colleagues' trial,[17] most deaths were attributed to either cancer or cardiovascular aetiologies, the pathogenesis of which has been well linked to inflammation.[19–21] The authors thus postulated that prolonged deep anaesthesia increases mortality by aggravating the inflammatory response to surgery. In support of that theory, a pilot study in orthopaedic joint replacement patients demonstrated that patients who received BIS-guided anaesthesia (target 45–60) showed a reduced postoperative inflammatory CRP response compared with deeper standard clinical practice.[22]

Evidence thus suggests that steroid administration, tight glucose control, and avoidance of deep anaesthesia may decrease perioperative morbidity by ameliorating the inflammatory response to surgery. Using a three-way factorial design, we thus tested the primary hypotheses that major perioperative morbidity is reduced by: (i) low-dose dexamethasone, (ii) intensive intraoperative glucose control, and (iii) lighter anaesthesia. We also tested the secondary hypotheses that each intervention reduces circulating concentrations of the inflammatory marker hsCRP and all-cause 1 yr mortality.

Methods

The study was conducted with approval of the Cleveland Clinic Institutional Review Board and written informed consent was obtained from all patients. Enrolment extended from March 2007 through July 2010.

The methods of DeLiT trial are presented in detail elsewhere.[23] Briefly, we enrolled patients having elective major non-cardiac surgery under general anaesthesia. The study was initially restricted to patients ≥50 yr old having open major vascular surgery, but was expanded to include patients ≥40 yr because of slow initial enrolment. We excluded patients who received i.v. or oral steroid therapy within 30 days, had any contraindications to the proposed interventions, had an ASA Physical Status (ASA PS) >IV, or were not fluent in English.

Randomization codes were generated by the PLAN procedure in SAS statistical software, and implemented using a concealed-allocation web-based system that was accessed by research physicians just before the planned surgery. Randomization was stratified according to the presence or absence of history of diabetes to ensure balance for each intervention comparison within diabetes status. Patients were randomly assigned to each of the following interventions:

(i) Dexamethasone or placebo: either i.v. dexamethasone 8 mg given 1–2 h before surgery (incision time), 4 mg on the first postoperative morning, and 2 mg on the second postoperative morning or comparable amounts of placebo at the same times.
(ii) Intensive or conventional glucose management: blood glucose concentrations were targeted to 4.4–6.1 mmol $litre^{-1}$ (80–110 mg dl^{-1}, intensive control) or 10–11.1 mmol $litre^{-1}$ (180–200 mg dl^{-1}, conventional control). Glucose control (mainly intraoperatively) began shortly after induction of anaesthesia using previously described protocols,[24] and continued through their first two postoperative hours. Glucose was subsequently managed per routine for the hospital ward [target of 3.9–8.3 mmol $litre^{-1}$ (70–150 mg dl^{-1})] or critical care unit [target of 4.4–6.7 mmol $litre^{-1}$ (80–120 mg dl^{-1})] to which they were admitted.
(iii) Lighter or deeper anaesthetic management: patients were assigned to a target BIS of 55 (lighter anaesthesia group) or to a target BIS of 35 (deeper anaesthesia group).

Clinicians were blinded to the dexamethasone but not to the glucose control or depth of anaesthesia interventions. However, patients and investigators responsible for assessing postoperative outcomes were fully blinded.

Our primary outcome was a collapsed composite endpoint (any *vs* none) defined as the occurrence of at least one of the 15 major complications before hospital discharge, including sepsis, severe surgical site infection, myocardial infarction, heart failure, stroke, unstable ventricular arrhythmias, pulmonary embolism, pneumonia, respiratory failure, dialysis dependent renal failure, large pleural or peritoneal effusions, major bleeding, major wound and surgical site healing complications, vascular graft thrombosis, and 30 day mortality.

Blood samples were collected before incision and on the first and second postoperative days, and were centrifuged in the cold at 3000*g*; plasma and serum were separated and stored in a freezer at −80°C. High-sensitivity CRP (hsCRP) was measured by an immunoturbidimetric method on an Abbott Architect ci8200 auto analyser (Abbott Laboratories, Abbott Park, IL, USA) using Kamiya hsCRP reagents (Kamiya Biomedical Co., Seattle, WA, USA). Each set of samples was accompanied by at least one set of bi-level plasma controls. These controls have a recorded inter- and intra-day coefficient of variation of <5%. The hsCRP results are reported in milligram per litre.

One-year mortality data were obtained from electronic medical records, the United States Social Security Index, or both and confirmed by direct telephone contact with patient/family.

Statistical analysis

Balance on baseline characteristics among the randomized groups was assessed separately for each intervention. Any variable with a standardized difference >0.3 in the absolute value was adjusted for when comparing intervention groups on outcomes. Analysis was intent-to-treat.

Primary outcome

We assessed the effects of all three interventions on the incidence of any major morbidity in a single logistic regression model. In the absence of a three-way or any two-way interactions among the interventions (all $P>0.10$), each main effect was tested by collapsing over the other interventions, after adjusting for imbalanced baseline variables. In addition, the effect of each intervention on each individual major complication component was assessed in separate logistic regressions (one for each component; the significance criterion was 0.0039/16=0.00024, a Bonferroni correction for 16 components, with interim-analysis α of 0.0039).

One year mortality

We assessed the effects of all three interventions on the incidence of 1 yr all-cause mortality in a single logistic regression model, adjusting for imbalanced baseline variables.

C-reactive protein

The effects of each randomized intervention on hsCRP and maximum postoperative change in hsCRP within two postoperative days from baseline were evaluated using linear regression.

Interim analyses

This trial followed a group sequential design in which four interim analyses were planned, using the gamma spending function[25] with gamma values of −3 and 0 for efficacy and futility, respectively. Results for the final analysis presented here used interim-adjusted confidence intervals (CIs) incorporating the *z*-statistic efficacy boundary of 2.884 for the $n=381$ patients included.[23]

Unless Bonferroni-corrected, all reported CIs use the interim-adjusted *z*-statistic of 2.884, corresponding to an α of 0.0039, and thus technically have 99.6% confidence. Throughout, we refer to them as '95% CIs' to indicate that the significance level was controlled at 5% for each hypothesis in the group sequential design.

Sample size considerations

The incidence of our primary outcome ranged from 15% to 19% from 2000 to 2003 in our institution's vascular surgery registry. However, we believed that these retrospective data underestimated the true incidence and expected a somewhat higher incidence because we planned to monitor the outcomes more closely than is done for retrospective data registeries. We thus assumed the true incidence to be 25% in the group receiving none of the three interventions. A maximum of 970 total patients were required to have 90% power at the 0.05 significance level to detect a 40% relative reduction on the primary outcome for the most effective intervention (whichever of the three), assuming effects of 20% and 10% for the other two interventions. If only one of the three factors had any effect, we had 90% power to detect a slightly narrower 37% relative reduction.

R 2.12.0 software (R Foundation for Statistical Computing, Vienna, Austria), SAS 9.2 software (SAS Institute, Cary, NC, USA), and East 5 software (Cytel, Inc., Cambridge, MA, USA) were used.

Results

The intervention groups for the randomized patients (Fig. 1) included in the final analysis were well balanced on most patient characteristics and baseline characteristics (Table 1). Only the presence of a history of coronary artery disease was imbalanced (standardized difference>0.3 in absolute value), and was therefore adjusted for in all analyses.

At the time of the first interim analysis ($n=242$), the Executive Committee decided to move the next analysis up from 50% to 37.5% of the planned enrolment based largely on logistical constraints but also with some concern for the possible futility of the interventions. The second analysis was conducted at $n=364$ (37.7% of planned maximum of 970); 17 additional patients were randomized, while outcomes data on the 364 were being collected and analysed. We thus report on all 381 randomized patients in this report.

The observed incidences of any major morbidity were very close to 20% for each randomized group. No three-way ($P=0.70$) or two-way interactions (all $P>0.52$) among the interventions were found on the primary outcome. Therefore, each of the three main effects was assessed marginally by collapsing over the other interventions in a single linear regression model adjusting for the history of coronary artery disease.

None of the interventions had an effect on major morbidity (all *P*-values >0.86, Table 2 and Fig. 2). At this second (and final) analysis ($n=381$), the group sequential efficacy and futility boundaries for the primary outcome were $P\leq0.0039$ and $P>0.7912$, respectively. Since each of the three interventions crossed the futility boundary, a recommendation was made to stop the trial (Fig. 3). In a sensitivity analysis, we also assessed the treatment effects using a more stringent criterion for baseline imbalance (a standardized difference of 0.20, thus adjusting for ASA status, type of surgery, and history of congestive heart failure in addition to coronary artery disease); results were nearly identical to our main analyses and reached the same conclusions.

The study was not powered to assess effects on the individual outcomes of the composite, as evidenced in Table 2 by the wide CIs (and some inestimable effects due to low incidence) for the individual components. No effect on 1 yr all-cause mortality was found for any of the three randomized interventions (all *P*-values >0.80, Table 2).

Glucose control intervention

Our glucose control intervention had no effect on the primary outcome of major morbidity, with odds ratio (95% CI) of 0.96 (0.45, 2.0), $P=0.86$. The median intraoperative time-weighted

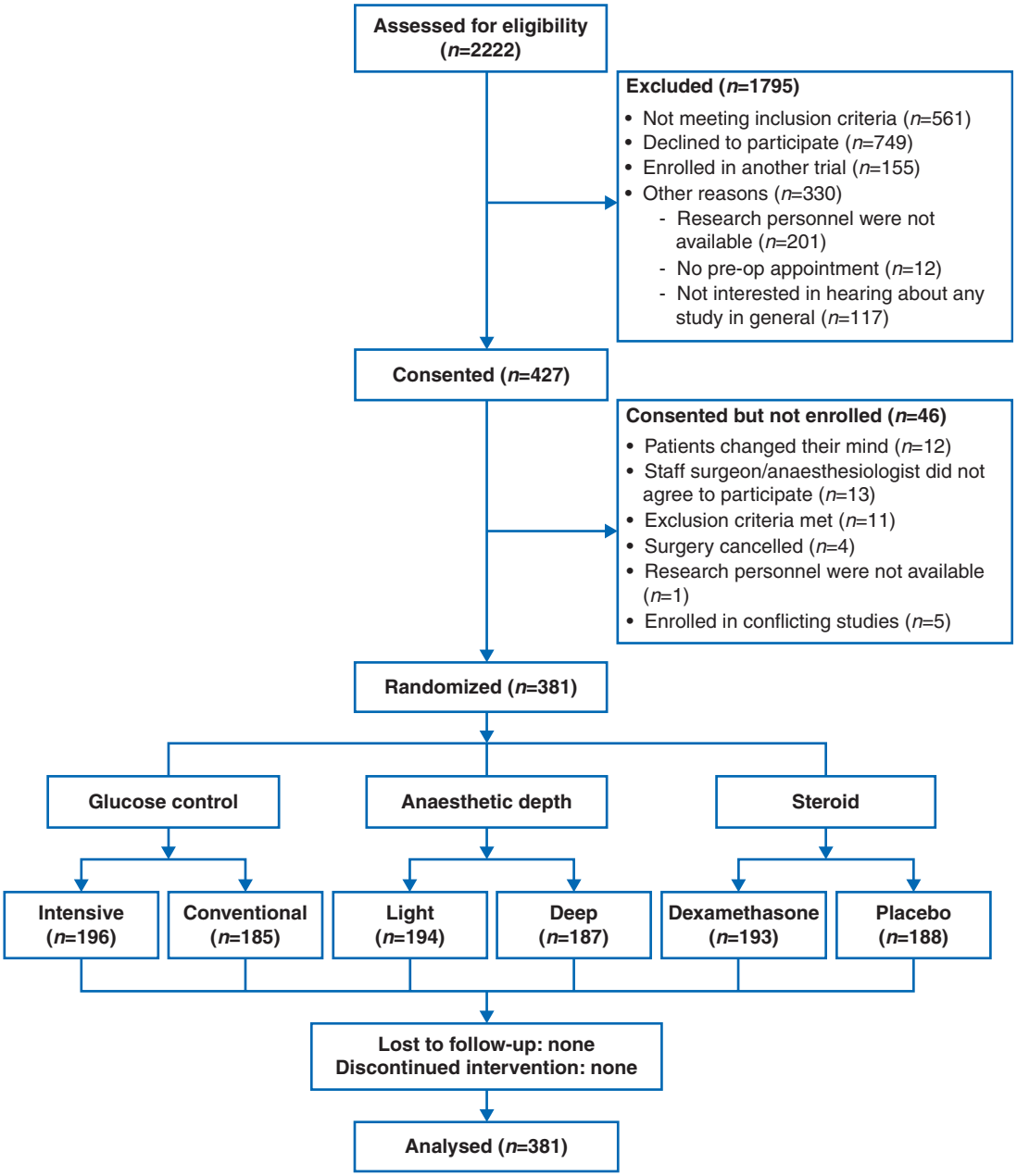

Fig 1 Study flow chart.

average glucose for the intensive glucose control patients [6.0 (Q1, Q3: 5.6, 6.7) mmol litre^{-1}, 108 (100, 121) mg dl^{-1}] was lower than for standard care patients [7.8 (6.9, 9.2) mmol litre^{-1}, 139 (124, 165) mg dl^{-1}] ($P<0.001$, Fig. 4A). However, no association was found between time-weighted average glucose and the composite of any major morbidity ($P=0.10$, Fig. 4B), with an estimated odds ratio of 1.13 (95% CI 0.91, 1.38) for a 1 mmol litre^{-1} increase in the time-weighted average glucose. More details on the results of the glucose control intervention are presented elsewhere,[24] but we note that there were no episodes of severe hypoglycaemia defined by a plasma glucose concentration of <2.2 mmol litre^{-1} (40 mg dl^{-1}). Only 15% ($n=29$) of the intensive and 2% ($n=4$) of the conventional glucose control patients had at least one episode of moderate hypoglycaemia (<4.0 mmol litre^{-1}≈72.7 mg dl^{-1}).

Anaesthetic depth intervention

Our anaesthetic depth intervention had no effect on the primary outcome of major morbidity, with odds ratio (95% CI) of 1.0 (0.49, 2.2), $P=0.90$. The overall median of individual

Table 1 Patient characteristics and baseline characteristics. Data are reported as mean (SD) or median (1st quartile, 3rd quartile). *1–2%; †3–5%; and ‡54–58% of patients had missing values. ASA, American Society of Anesthesiologists Physical Status; BIS, bispectral index; MAP, mean arterial pressure; PTCA, percutaneous transluminal coronary angioplasty; TWA, time-weighted average

Variables	Glucose control		Anaesthetic depth		Steroids	
	Intensive (*n*=196)	Conventional (*n*=185)	Light (*n*=194)	Deep (*n*=187)	Dexamethasone (*n*=193)	Placebo (*n*=188)
Age (yr)	64 (11)	64 (11)	63 (11)	65 (12)	64 (11)	64 (12)
Gender (male) (%)	64	70	63	70	68	65
Race (White) (%)	94*	96	95*	95	97*	94
ASA (%)						
II	24	30	32	21	27	26
III	65	60	57	68	63	62
IV	11	10	11	11	10	12
BMI (kg m^{-2})	28 (25, 31)	27 (24, 31)	27 (24, 30)	27 (24, 32)	27 (24, 31)	27 (24, 31)
Smoking (%)†						
Yes	30	29	28	31	27	31
Quit	36	33	32	38	36	34
No	34	38	40	32	37	35
Drinks (*n*/week)‡	0 (0, 3)	1 (0, 3)	1 (0, 3)	0 (0, 4)	1 (0, 3)	1 (0, 4)
Diabetes stratum (Yes) (%)	28	26	27	27	26	28
Surgery type (%)						
Abdominal aortic aneurysm	16	15	17	14	17	14
Colectomy	28	31	30	29	32	27
Cystectomy	17	19	20	16	18	19
Peripheral revascularization	16	15	15	16	12	19
Whipples	20	17	15	23	18	20
Other	2	2	3	2	3	1
Previous medical history (%)						
Chronic obstructive pulmonary disease	7	6	6	7	8	6
Asthma	6	5	5	6	4	7
Stroke	5	4	3	5	5	4
Transient ischaemic attack	3	2	3	2	3	2
Hypertension	63	61	59	64	60	63
Hyperlipidaemia	50	48	47	51	50	48
Congestive heart failure	4	6	6	5	3	8
Coronary artery disease	30	27	21	36	25	32
Myocardial infraction	16	14	13	18	14	16
Coronary artery bypass graft	13	10	8	14	8	14
PTCA	11	12	10	13	8	14
Rhythm disturbance	10	8	10	9	10	8
Valvular heart disease	4	5	4	5	4	5
Chronic renal insufficiency	4	4	5	3	3	5
Hepatic disease	3	3	3	3	2	4
Preoperative						
MAP (mm Hg)	94 (12)	92 (12)	93 (11)	93 (13)	92 (12)	94 (12)
Heart rate (beats min^{-1})†	75 (13)	75 (13)	75 (13)	76 (13)	76 (14)	74 (13)
Blood glucose (mmol $litre^{-1}$)*	5.7 (4.8, 6.8)	5.4 (4.8, 6.4)	5.5 (4.7, 6.5)	5.7 (4.9, 6.6)	5.4 (4.7, 6.4)	5.8 (4.9, 6.8)
Intraoperative						
Anaesthesia duration (h)	5.6 (2.4)	6.0 (2.1)	5.9 (2.4)	5.7 (2.2)	5.9 (2.3)	5.7 (2.2)
Estimated blood loss (litre)	0.5 (0.2, 1)	0.5 (0.2, 1.2)	0.5 (0.2, 1.2)	0.5 (0.2, 1)	0.5 (0.2, 1.2)	0.5 (0.2, 1)
Urine output (ml)†	438 (204, 730)	450 (273, 700)	450 (222, 700)*	452 (248, 770)	460 (250, 759)	418 (216, 660)
Crystalloid (litre)	4.0 (2.9, 5.0)	4.0 (3.0, 5.5)	4.1 (2.9, 5.5)	4.0 (3.0, 5.0)	4.2 (3.1, 5.6)	3.8 (2.8, 5.0)
Colloid (litre)	0.8 (0.6)	0.9 (0.6)	1 (0.5, 1)	1 (0.5, 1)	0.8 (0.6)	0.8 (0.6)

Continued

Table 1 *Continued*

Variables	Glucose control		Anaesthetic depth		Steroids	
	Intensive (n=196)	Conventional (n=185)	Light (n=194)	Deep (n=187)	Dexamethasone (n=193)	Placebo (n=188)
TWA glucose (mmol litre^{-1})	6.3 (1.1)	8.1 (1.8)	7.1 (1.7)	7.1 (1.7)	7.4 (1.7)	6.8 (1.7)
% time glucose 80–110 mg dl^{-1} (4.4–6.1 mmol litre^{-1})	49 (28, 71)	3 (0, 25)	30 (0, 57)	24 (0, 56)	16 (0, 45)	35 (7, 72)
Median BIS	47 (7.0)	47 (7.4)	50 (6.0)	44 (6.9)	47 (7.1)	47 (7.3)
% of time BIS<45	35 (10, 73)	37 (10, 69)	16 (4, 40)	66 (36, 86)	41 (9, 73)	34 (11, 68)

patient median BIS values (which included minute-by-minute BIS values from 15 min after induction to 15 min before emergence) was greater in patients under lighter anaesthetic management than those under deeper anaesthetic management [50 (6.0) *vs* 44 (6.9), P<0.001, Fig. 5A]. Also, patients under lighter anaesthetic management spent a smaller fraction of their time with BIS values <45 [16 (4, 40)% *vs* 66 (36, 86)%, P<0.001, Fig. 5C]. However, no association was found between the incidence of any major morbidity and median patient BIS (P=0.68, Fig. 5B) or per cent of time spent under deep anaesthesia, BIS<45 (P=0.98, Fig. 5D), with estimated odds ratios (95% CI) of 0.93 (0.55, 1.55) and 1.00 (0.90, 1.12), respectively, for a 10 unit increase.

Dexamethasone intervention and CRP analysis

Our steroid intervention also had no effect on the primary outcome of major morbidity, with odds ratio (95% CI) of 0.96 (0.45, 2.0), P=0.87. The mean hsCRP levels at POD1 and POD2 (Table 3, Fig. 6A), and the mean changes in CRP from baseline (Table 3, Fig. 6B) were significantly lower in patients given dexamethasone than placebo (all P-values <0.001); all groups had similar median hsCRP at baseline. Neither the intensive *vs* conventional glucose control nor the light *vs* deep anaesthetic depth interventions affected either mean postoperative hsCRP or mean change in hsCRP (smallest P-value was 0.56). However, after adjusting for the three interventions and history of coronary artery disease, change in hsCRP from baseline to the maximum value observed on POD1 and 2 was associated with a slight increase in major morbidity (P=0.002), with an estimated odds ratios of 1.06 (95% CI: 1.0, 1.12) for a 10 mg litre^{-1} increase in the change in hsCRP (Fig. 6C).

Discussion

It is well established that surgery produces an inflammatory response that is proportionate to tissue injury.[1 2] Our results are consistent in that major surgery provoked an intense inflammatory response, as characterized by a roughly 30-fold elevation in plasma hsCRP concentrations. Many studies have examined preoperative levels of hsCRP in a variety of non-cardiac surgical populations,[26–28] but few have quantified the inflammatory response to non-cardiac surgery *per se*.[29 30] Amar and colleagues[29] reported a four- to10-fold increase in hsCRP on the first postoperative day in 195 patients undergoing thoracic non-cardiac surgery. We extend this work by showing that the change in hsCRP from baseline to the maximum value observed on the first and second postoperative days is associated with major postoperative morbidity which corroborates the findings of Amar and colleagues[29] and Kouvelos and colleagues.[30]

It is also well established that perioperative steroid administration blunts inflammation.[8 9 31] As might thus be expected, steroids significantly ameliorated the hsCRP response to tissue injury. Surprisingly, though, steroid-induced amelioration of the inflammatory response to surgery did not reduce postoperative complications.

Large-dose steroids have been shown to improve postoperative outcomes in patients undergoing cardiac (n=235) or colorectal (n=20) surgery.[8 32] However, clinicians were understandably concerned about potential side-effects of such large doses.[6] Subsequent work by Kilger and colleagues[31] (n=91) suggested that much smaller doses—which are presumably safer—are also effective. The dose we chose is similar to that used by Kilger and colleagues,[31] although we used a total of 14 mg of dexamethasone rather than hydrocortisone. The dose is also similar to Bisgaard and colleagues[9] who found that 8 mg of dexamethasone given i.v. to patients (n=88) before their laparoscopic cholecystectomy reduced CRP concentrations and improved postoperative pain, fatigue, nausea and vomiting, and faster return to recreational activities.

Steroid doses similar to the one we tested improved postoperative fatigue and duration of convalescence,[9] whereas we detected no reduction in a composite of serious complications. It remains possible that a larger dose or a different kind of steroid might have been more effective;[33] this argument is supported by the fact that while the typical CRP response to surgery was ameliorated in our patients, the increase was nonetheless substantial in both groups. Our study is the largest to evaluate small-to-moderate-dose steroids in general surgical patients. Furthermore, enrolment was restricted to patients undergoing major surgery. And finally, most had substantial baseline co-morbidity (~70% were ASA PS III or IV) and, in fact, about 20% of our patients experienced at least one component of our composite outcome. We thus had considerable power to detect steroid-induced benefit had there been one.

Table 2 Effects of interventions on composite and individual major morbidities and 1 yr mortality (n=381). Adjusting for the history of coronary artery disease. Composite components presented as number (%).*For the primary outcome (any major morbidity), the CIs were interim-adjusted using a z-statistic criterion of 2.884, corresponding to the interim analysis P-value boundary for efficacy ($P \leq 0.0039$); the futility boundary was $P > 0.7912$. For the individual morbidities, CIs were further adjusted for multiple testing; the significance criterion was 0.0039/16=0.00024. †Inestimable: no odds ratio estimate obtainable due to very low incidence

Outcome	Glucose control				Anaesthetic depth				Steroids			
	Intensive (n=196)	Conventional (n=185)	OR (95% CI)*	P-value*	Light (n=194)	Deep (n=187)	OR (95% CI)*	P-value*	Dexamethasone (n=193)	Placebo (n=188)	OR (95% CI)*	P-value*
Any major morbidity	38 (19.4)	37 (20)	0.96 (0.45, 2.0)	0.86	38 (19.6)	37 (19.8)	1.0 (0.49, 2.2)	0.90	37 (19.2)	38 (20.2)	0.96 (0.45, 2.0)	0.87
Individual morbidities												
30 day mortality	4 (2)	4 (2.2)	0.95 (0.07, 13)	0.95	3 (1.5)	5 (2.7)	0.65 (0.04, 10)	0.57	3 (1.6)	5 (2.7)	0.61 (0.04, 9.4)	0.51
Ventricular arrhythmias	2 (1)	2 (1.1)	1.0 (0.02, 46)	0.98	1 (0.5)	3 (1.6)	0.49 (0.01, 38)	0.55	1 (0.5)	3 (1.6)	0.38 (<0.001, 29)	0.42
Bleeding	4 (2)	4 (2.2)	0.95 (0.07, 13)	0.94	4 (2.1)	4 (2.1)	0.85 (0.06, 12)	0.83	5 (2.6)	3 (1.6)	1.6 (0.10, 24)	0.55
Bowel and surgical anastomosis stricture/obstruction or anastomotic leak	3 (1.5)	5 (2.7)	0.60 (0.04, 9.2)	0.49	6 (3.1)	2 (1.1)	2.4 (0.11, 49)	0.30	4 (2.1)	4 (2.1)	0.88 (0.06, 12)	0.86
Pulmonary oedema and congestive heart failure	4 (2)	2 (1.1)	1.8 (0.07, 45)	0.52	2 (1)	4 (2.1)	0.62 (0.02, 17)	0.60	4 (2.1)	2 (1.1)	2.1 (0.08, 55)	0.39
Large peritoneal/pleural effusion	0 (0)	2 (1.1)	Inestimable†	0.96	1 (0.5)	1 (0.5)	1.2 (0.01, 287)	0.88	1 (0.5)	1 (0.5)	1.2 (0.01, 246)	0.89
Pulmonary emboli	0 (0)	0 (0)	Inestimable†	>0.99	0 (0)	0 (0)	Inestimable†	>0.99	0 (0)	0 (0)	Inestimable†	>0.99
Fistula	1 (0.5)	2 (1.1)	0.48 (0.01, 44)	0.55	1 (0.5)	2 (1.1)	0.48 (<0.001, 47)	0.56	1 (0.5)	2 (1.1)	0.50 (0.01, 46)	0.57
Deep or organ/space surgical site infection	17 (8.7)	18 (9.7)	0.88 (0.24, 3.2)	0.72	18 (9.3)	17 (9.1)	0.96 (0.25, 3.6)	0.90	21 (10.9)	14 (7.4)	1.5 (0.39, 5.6)	0.28
Myocardial infarction	2 (1)	4 (2.2)	0.45 (0.02, 11)	0.37	4 (2.1)	2 (1.1)	2.4 (0.09, 64)	0.33	2 (1)	4 (2.1)	0.56 (0.02, 14)	0.51
Pneumonia	5 (2.6)	3 (1.6)	1.6 (0.11, 24)	0.53	2 (1)	6 (3.2)	0.30 (0.01, 6.3)	0.15	3 (1.6)	5 (2.7)	0.55 (0.04, 8.4)	0.43
Renal failure	3 (1.5)	4 (2.2)	0.72 (0.04, 12)	0.68	3 (1.5)	4 (2.1)	0.70 (0.04, 12)	0.65	2 (1)	5 (2.7)	0.38 (0.02, 8.6)	0.26
Respiratory failure	9 (4.6)	5 (2.7)	1.8 (0.22, 15)	0.31	4 (2.1)	10 (5.3)	0.38 (0.04, 3.5)	0.11	5 (2.6)	9 (4.8)	0.52 (0.06, 4.2)	0.25
Sepsis	4 (2)	2 (1.1)	1.9 (0.08, 47)	0.46	2 (1)	4 (2.1)	0.49 (0.02, 12)	0.41	3 (1.6)	3 (1.6)	0.95 (0.05, 20)	0.95
Stroke	0 (0)	0 (0)	Inestimable†	>0.99	0 (0)	0 (0)	Inestimable†	>0.99	0 (0)	0 (0)	Inestimable†	>0.99
Vascular graft thrombosis	1 (0.5)	3 (1.6)	0.30 (<0.001, 22)	0.31	2 (1)	2 (1.1)	1.4 (0.03, 65)	0.73	1 (0.5)	3 (1.6)	0.42 (0.01, 31)	0.46
1 yr mortality	24 (12)	21 (11)	0.92 (0.37, 2.3)	0.80	22 (11)	23 (12)	1.1 (0.42, 2.7)	0.87	22 (11)	23 (12)	1.1 (0.43, 2.7)	0.84

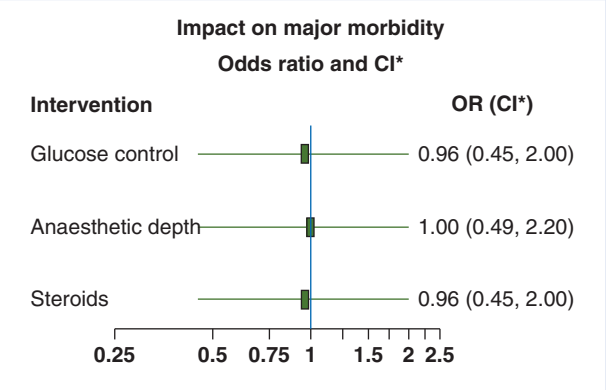

Fig 2 Odds ratios of any major morbidity for each intervention, adjusting for history of coronary artery disease. *CIs were interim-adjusted using a *z*-statistic criterion of 2.884, corresponding to the *P*-value boundary for efficacy ($P \leq 0.0039$).

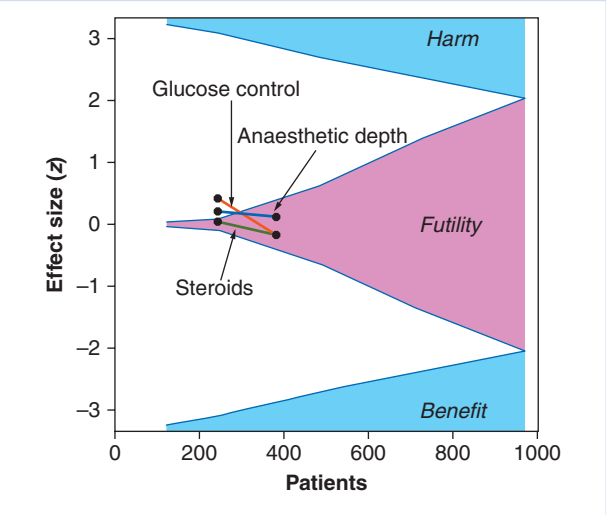

Fig 3 DeLiT interim monitoring results for the primary outcome of any major morbidity at $n=242$ and $n=381$. The group sequential futility boundary (pink region) was crossed for each of the three interventions at the second interim analysis ($n=381$); the trial was therefore stopped for futility. Vertical axis is the *z*-statistic corresponding to the standardized treatment effect estimated at each interim analysis; negative values indicate efficacy (significant if reaching lower blue region), while positive values indicate harm (significant if reaching upper blue region).

In contrast to steroid administration—and somewhat surprisingly[10]—hsCRP was unchanged by tight glucose control. But there are many mechanisms besides inflammatory modulation by which glucose control could reduce morbidity after major surgery. And as might thus be expected, benefit from tight glucose control has been demonstrated in various populations.[12 34–36] In our surgical patients, though, no benefit (or harm) was detected. Our results are consistent with previous reports,[13 15] suggesting that tight intraoperative glucose control alone has little effect on the risk of serious complications after major non-cardiac surgery.

The blood glucose concentrations we targeted were those most commonly studied in critical care[12] and cardiac surgery[13] patients when our study started in early 2007. The ideal perioperative target in non-cardiac surgery remains unknown, and various target concentrations have been used since our study start date.[15] Time-weighted average plasma glucose concentrations in patients assigned to tight control averaged 6.0 (inter-quartile range: 5.6, 6.7) mmol litre^{-1} [108 (100, 121) mg dl^{-1}] which was at the high end of our target range of 4.4–6.1 mmol litre^{-1} (80–110 mg dl^{-1}).[24] Glucose concentrations in the conventional management group were significantly greater, with a time-weighted average of 7.8 mmol litre^{-1} (139 mg dl^{-1}). The associated wide inter-quartile range of 6.9–9.2 mmol litre^{-1} (124, 165 mg dl^{-1}) resulted because, per protocol, we did not intervene for these patients until glucose went above the intervention threshold; but even without treatment, most never did. Thus, a larger difference in glucose concentrations could only be obtained by more aggressive treatment in patients assigned to intensive treatment. The difficulty with this approach—even assuming it improved outcome—is that tighter glucose control increases the risk of hypoglycaemia.[14 15 37 38] We did not observe hypoglycaemia, defined by glucose <2.2 mmol litre^{-1} (40 mg dl^{-1}), possibly because of the dynamic nature of our insulin infusion algorithm, the relatively frequent glucose concentration determinations (every 30–60 min), and vigilance of the investigators and clinicians.[24]

We, like most investigators, used the same target glucose concentrations for diabetic and non-diabetic patients. But in critical care patients, intensive glucose control appears to reduce mortality except in diabetics.[39] Similarly, Krinsley[40] reports that hyperglycaemia is associated with higher mortality in critical care patients without diabetes compared with those with diabetes. Furthermore, Egi and colleagues[41] found that lower blood glucose concentrations were associated with increased mortality in diabetic critical care patients. Our study was underpowered to assess the interaction between intensive glucose control and diabetic status. A differential effect of tight glucose control in diabetic and non-diabetic patients thus remains possible—but would not change our overall conclusion that tight intraoperative glucose control does not reduce the risk of severe morbidity after major non-cardiac surgery.

Randomized trials have suggested that BIS-guided anaesthesia speeds recovery, improves haemodynamic control, and reduces respiratory complications, nausea and vomiting, and the duration of hospitalization.[42–44] Our expectation that light anaesthesia would reduce inflammation was largely based on a report by Kerssens and Sebel[22] who found that the CRP response to joint replacement surgery was moderated when anaesthesia was guided to a BIS target of 45–60 rather than deeper hypnosis (regretfully, that study has not since appeared in a peer-reviewed

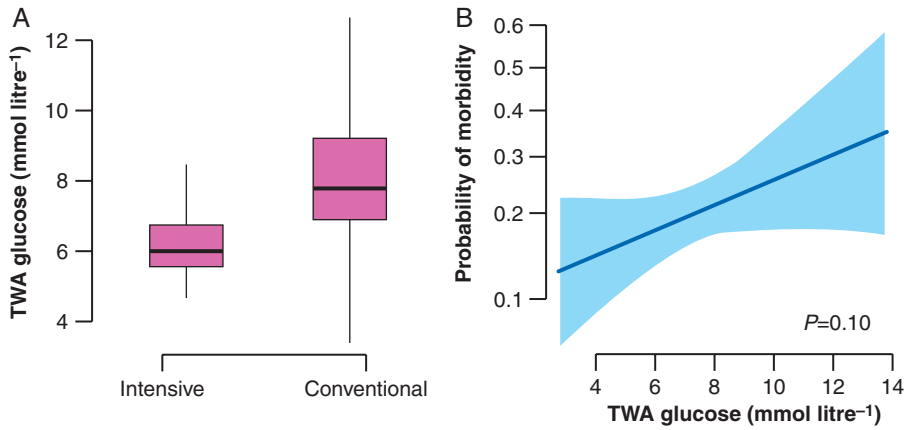

Fig 4 Boxplots of (A) time-weighted average of intraoperative glucose values stratified by glucose control intervention (intensive *vs* conventional); and (B) probability of postoperative composite morbidity (on logit scale to correspond to the logistic regression analysis) *vs* the time-weighted glucose from a smoothed univariable logistic regression.

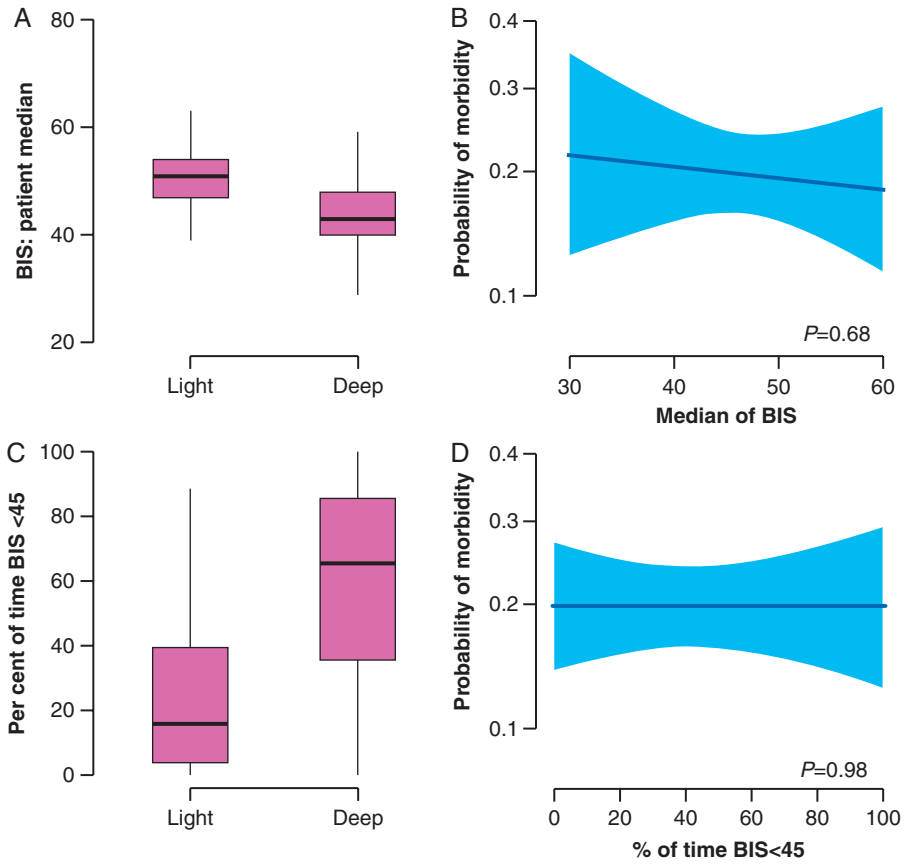

Fig 5 Boxplots of (A) median BIS value during the period from 15 min after induction of anaesthesia until 15 min before the end of anaesthesia in patients assigned to light or deep anaesthesia; (B) probability of postoperative composite morbidity (on logit scale to correspond to the logistic regression analysis) *vs* median BIS; (C) per cent of time BIS<45 by intervention; and (D) probability of postoperative composite morbidity (logit scale) *vs* per cent of time BIS<45 from smoothed univariable logistic regressions.

Table 3 Summary statistics and treatment effects on hsCRP (mg litre^{-1}) concentrations. Statistics are median (Q1, Q3) or mean (SD), as appropriate. hsCRP, high-sensitivity C-reactive protein. *n=5, 22, 35, 25, 37, and 15 patients had missing hsCRP at baseline, POD1, POD2, change in hsCRP from baseline to POD1, POD2, and maximum postoperative hsCRP, respectively. †$P<0.001$ *vs* saline (adjusting for other interventions); neither glucose control nor anaesthetic depth affected any of the changes from baseline hsCRP (all $P>0.05$)

hsCRP* (mg litre^{-1})	Steroids		Glucose		Anaesthetic depth	
	Dexamethasone (n=193)	Placebo (n=188)	Intensive (n=196)	Conventional (n=185)	Light (n=194)	Deep (n=187)
Baseline	4 (2, 10)	3 (2, 7)	4 (2, 9)	3 (2, 9)	4 (2, 8)	4 (2, 11)
POD1	84 (46)	110 (48)	96 (48)	97 (49)	95 (47)	98 (50)
POD2	113 (67)	165 (72)	137 (76)	140 (72)	138 (73)	140 (75)
Changes in CRP from baseline						
To POD1	75 (45)†	111 (47)	87 (48)	88 (47)	88 (46)	87 (49)
To POD2	104 (65)†	156 (70)	128 (75)	131 (70)	130 (72)	129 (73)
To max POD1,2	108 (64)†	155 (69)	130 (72)	133 (68)	130 (70)	132 (70)

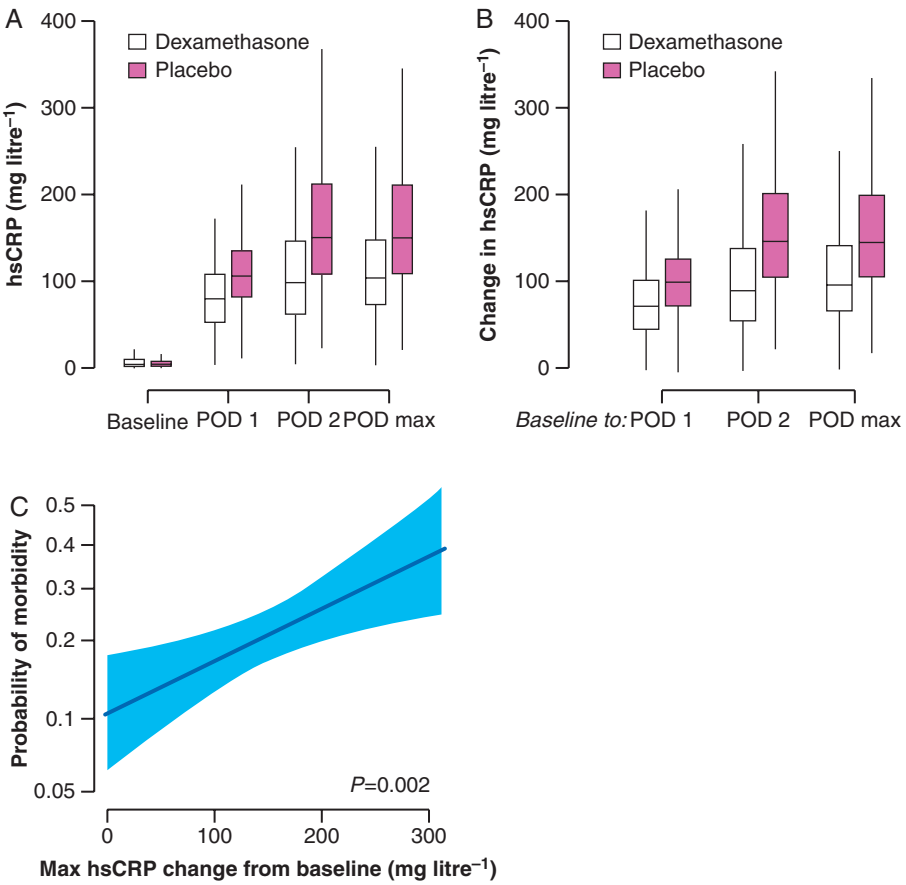

Fig 6 Boxplots of (A) CRP values over time stratified by steroid intervention (dexamethasone *vs* placebo); (B) changes in CRP from baseline to postoperative day 1 (POD1) and 2 (POD2), and maximum of POD1 and 2, by intervention; and (C) probability of postoperative composite morbidity (on logit scale to correspond to the logistic regression analysis) *vs* change in CRP from baseline to maximum (POD1, POD2).

journal). In distinct contrast, we found that hsCRP concentrations were similar in a large group of patients who were randomly assigned to light *vs* deep hypnosis. Perhaps unsurprisingly, we also found no difference in the incidence of major complications between the two groups. Thus, while maintaining a light hypnotic plane during anaesthesia appears to provide substantial benefits,[42 43] preventing major morbidity is not among them.

As our three interventions did not result in a difference in the primary outcome, it is thus unsurprising that we also did not show any difference in 1 yr mortality. Long-term mortality outcome has not been well studied for tight glucose control or steroids perioperative interventions. On the other hand, many observational and retrospective studies have suggested an association between depth of anaesthesia and 1 yr mortality;[18 44] we were unable to show the same results in our randomized trial. That said, it should be noted that 1 yr mortality was a secondary outcome and our trial was not powered to detect a statistically significant difference among study groups.

Although we had 90% power to detect a relative reduction ranging from 37% to 40% for the strongest of the three effects studied, smaller effects would clearly be important as well, and the study did not have sufficient power to detect them. While our results are very non-significant, the CIs for our estimated treatment effects are wide and theoretically consistent with either no effect or up to a doubling (or halving) of the incidence of complications. However, since our observed effects were so close to zero, conditional power results indicated an extremely low probability of finding a significant effect even if the trial would have continued to the maximum planned sample size (n=970).

We did not have sufficient power to detect interactions among the interventions, which would have required a planned maximum sample size of ~4000 patients. But given the absence of main effects, interactions would have been quite unexpected. In fact, the interaction P-values were very non-significant (three-way interaction P=0.70, and most significant two-way interaction P=0.52), such that there was very little evidence of any interactions in the observed data, and thus very little evidence that any of the interventions varied as a function of one another.

The ideal requirements for a composite outcome may not have been completely met in this study, that is, that components have equal clinical severity, similar incidence, and similar treatment effects.[45 46] However, the components of our composite had a similar incidence and were of roughly comparable clinical severity (Table 2), although mortality is certainly worse than the others. Our composite is a minor modification of the composite outcome used by Brandstrup and colleagues[47] and Nisanevich and colleagues.[48] That said, the use of a composite adverse outcome indicator rather than independently evaluating specific complications likely reduces the chance of type 2 error. More importantly, using any single outcome may not capture the entire effect of any of our interventions or the complex disease processes.

In summary, major non-cardiac surgery induces marked inflammation. Among our three interventions—dexamethasone, tight glucose control, and light anaesthesia—only dexamethasone reduced the inflammatory response to surgery, measured by hsCRP. However, we found no evidence that any of the studied interventions reduced the risk of major morbidity or 1 yr all-cause mortality.

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Declaration of interest

None declared.

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