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Clinical Practice

Intraoperative dexamethasone does not increase the risk of postoperative wound infection: a propensity score-matched *post hoc* analysis of the ENIGMA-II trial (EnDEX)

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Abstract

Background. In a *post hoc* analysis of the ENIGMA-II trial, we sought to determine whether intraoperative dexamethasone was associated with adverse safety outcomes.
Methods. Inverse probability weighting with estimated propensity scores was used to determine the association of dexamethasone administration with postoperative infection, quality of recovery, and adverse safety outcomes for 5499 of the 7112 non-cardiac surgery subjects enrolled in ENIGMA-II.
Results. Dexamethasone was administered to 2178 (40%) of the 5499 subjects included in this analysis and was not associated with wound infection [189 (8.7%) *vs* 275 (8.3%); propensity score-adjusted relative risk (RR) 1.10; 95% confidence interval (CI) 0.89–1.34; $P=0.38$], severe postoperative nausea and vomiting on day 1 [242 (7.3%) *vs* 189 (8.7%); propensity score-adjusted RR 1.06; 95% CI 0.86–1.30; $P=0.59$], quality of recovery score [median 14, interquartile range (IQR) 12–15, *vs* median 14, IQR 12–16, $P=0.10$), length of stay in the postanaesthesia care unit [propensity score-adjusted median (IQR) 2.0 (1.3, 2.9) *vs* 1.9 (1.3, 3.1), $P=0.60$], or the primary outcome of the main trial. Dexamethasone administration was associated with a decrease in fever on days 1–3 [182 (8.4%) *vs* 488 (14.7%); RR 0.61; 95% CI 0.5–0.74; $P<0.001$] and shorter lengths of stay in

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hospital [propensity score-adjusted median (IQR) 5.0 (2.9, 8.2) *vs* 5.3 (3.1, 9.1), $P<0.001$]. Neither diabetes mellitus nor surgical wound contamination status altered these outcomes.

Conclusion. Dexamethasone administration to high-risk non-cardiac surgical patients did not increase the risk of postoperative wound infection or other adverse events up to day 30, and appears to be safe in patients either with or without diabetes mellitus.

Clinical trial registration. NCT00430989.

Key words: dexamethasone; nitrous oxide; postoperative nausea and vomiting; surgical wound infection

Editor's key points

- Dexamethasone is widely used to prevent and treat postoperative nausea and vomiting.
- The association of intraoperative dexamethasone with postoperative infection, quality of recovery, and adverse safety events was tested in a *post hoc* subgroup analysis of the ENIGMA-II trial.
- Dexamethasone was not associated with postoperative infection or adverse events in a group of high-risk non-cardiac surgical patients.

The synthetic glucocorticoid dexamethasone is widely used as an antiemetic in the perioperative period.[1] It is inexpensive, effective, and long-acting and is recommended as a first-line antiemetic in recent international guidelines.[2] However, in common with other glucocorticoids, it has significant metabolic and immunological side-effects.[3] Immune suppression and hyperglycaemia[4] are the cardinal concerns in the perioperative period, because both may contribute to an increased risk of infection. Despite widespread use of dexamethasone amongst surgical patients, there remains uncertainty as to whether this is associated with increased risk of postoperative infection.[5 6]

The ENIGMA-II trial was a large international randomized controlled trial examining the postoperative cardiac events after 70% nitrous oxide in high-risk adults undergoing non-cardiac surgery; the primary end point was a composite outcome of death and major non-fatal cardiovascular events up to 30 days after surgery.[7] A substantial proportion of patients recruited to the ENIGMA-II trial received intraoperative dexamethasone as a part of their routine perioperative care. The ENIGMA-II data set, therefore, provides an opportunity for further evaluation of the association of dexamethasone administration and postoperative infection in a prospectively collected data set with robust outcome methodology. The primary aim of this *post hoc* subanalysis was to explore the association between intraoperative administration of dexamethasone and wound infection. Our *a priori* hypothesis was that patients receiving dexamethasone were at higher risk of postoperative wound infection, and the subgroups at greatest risk would be patients with diabetes mellitus or a contaminated surgical field. We also sought to explore the association of dexamethasone with fever on days 1–3 after surgery, severe postoperative nausea and vomiting (PONV) on day 1, length of hospital stay, quality of recovery (QoR), and the composite primary end point of the main trial.

Methods

The design and rationale of the ENIGMA-II trial has been published (ClinicalTrials.gov identifier NCT00430989).[8] In summary, patients were eligible for inclusion if they were ≥45 yr old, undergoing elective non-cardiac surgery for 2 h or longer, and were considered to be at high risk of cardiac events. Patients were excluded in the following circumstances: (i) if they were having cardiac surgery; (ii) if they had marked impairment of gaseous exchange requiring an inspired oxygen fraction (FIO_2) >0.5 during surgery; (iii) in a specific circumstance where nitrous oxide use is contraindicated (volvulus, bowel obstruction, or elevated intracranial pressure); or (iv) where nitrous oxide is not available for clinical use. The primary end point was a composite outcome of death and major non-fatal cardiovascular events up to 30 days after surgery. We also collected data regarding wound infection, duration of stay in the intensive care unit (ICU) and hospital, and severe PONV. Severe PONV was defined as two or more episodes of nausea, vomiting, or both at least 6 h apart, or requiring three or more doses of rescue antiemetics of two or more different classes in any 24 h during the first 3 days after surgery. Quality of recovery (QoR) score was recorded on day 1. Body temperature was measure from day 1 to 3. Fever was defined as core temperature ≥38 °C.

All centres obtained institutional review board approval, and all patients provided written informed consent for enrolment in the original trial. This substudy and analysis was not planned at the time of initiation of the trial. It followed a predefined analysis plan, which was approved by the steering committee of the main trial. Patients were randomly assigned to receive a general anaesthetic either with or without nitrous oxide in the gas mixture. Treatment assignment was stratified by site with permuted blocks. Attending anaesthetists were aware of the group assignments, but subjects, the operating team, research coordinators who conducted the postoperative interviews, and end point adjudicators were unaware of treatment group. For subjects assigned to receive nitrous oxide, anaesthetists were advised to give nitrous oxide at an inspired concentration of 70% in 30% oxygen, and for patients assigned not to receive nitrous oxide, anaesthetists were advised to give an air–oxygen gas mixture with $FIO_2=0.3$ for maintenance of anaesthesia and tracheal intubation or laryngeal mask insertion. The allocated gas concentrations were then continued until the completion of surgery. Prophylactic antibiotics were administered according to local practice, and usual efforts to avoid intraoperative hypothermia were made. Standard anaesthetic and other perioperative care was given. There was no restriction on the use of neuraxial or other regional anaesthetic techniques. Anaesthetic depth was adjusted according to clinical judgement, with guidance from monitoring. Subjects were reviewed daily while in

hospital and were contacted by telephone at 30 days after surgery. The present substudy and analysis focused on the effect of dexamethasone on postoperative wound infection. The substudy was planned after two-thirds of subjects had been recruited to the trial. A statistical analysis plan was prepared and approved by the steering committee before trial completion.

Data analysis

Baseline subject characteristics were summarized as the mean (SD) for continuous variables and the number (percentage) for categorical variables, and were compared between intervention groups using χ^2 tests and analysis of variance, respectively. Dexamethasone administration was at the discretion of the attending anaesthetist. Given that dexamethasone was not randomly assigned to subjects, in order to try to reduce bias in comparing non-randomized treatments, a propensity score-based approach was applied. A propensity score is the probability of receiving a treatment, modelled as a function of observed variables, and can be used to adjust for confounding of the treatment–outcome relationship by observed characteristics.[9 10] The propensity score for this analysis was the probability of receiving dexamethasone, estimated using a logistic regression model of dexamethasone receipt, adjusting for observed variables.[9 10] Main effects for all baseline characteristics listed in Table 1 were included in the propensity score model. We used an inverse probability of treatment weighting approach, whereby each subject was weighted by the inverse of the probability that they received their actual treatment, with this probability calculated using the propensity score. In the weighted data, measured characteristics are balanced between treatment groups, although unmeasured characteristics may not be balanced. The balance of measured characteristics was assessed in the unweighted and weighted samples using standardized differences, which are the difference of means (percentages for categorical variables) between treatment groups divided by the SD.[11] Standardized differences >10% are generally considered to represent meaningful imbalances.[12]

A key assumption of propensity score approaches is the positivity assumption, which implies that each subject has a non-zero probability of receiving each treatment.[10] To ensure satisfaction of this assumption, data from countries in which fewer than five subjects or ≤5% of subjects received dexamethasone were removed from the analysis. The propensity score assumption also implies a 'common support' condition, which states that there must be comparable subjects in each treatment group.[10] Subjects with no comparable subject in the other intervention group (where comparability was assessed by directly comparing propensity scores) were thus excluded, because the effect of the intervention cannot be estimated reliably for such patients.

To estimate the association between dexamethasone and each wound infection, the composite end point, PONV on day 1 after surgery, and fever on any of days 1–3 after surgery, relative risks (RR) and confidence intervals (CI) were estimated from weighted and unweighted binary regression models including dexamethasone as the sole predictor. To compare the quality of recovery between dexamethasone groups, weighted and unweighted linear regression models for the logarithm of QoR scores were fitted. In the weighted models, observations from each subject were weighted by the inverse of the probability of receiving the treatment they actually received. In order to assess the sensitivity of the results to observations with large weights, weights were truncated at the 99th percentile and the weighted analyses repeated. Differences in the rates of wound infection across diabetic status and surgical contamination status cohorts were assessed using a subgroup-by-dexamethasone interaction term in the binary regression models. Lengths of stay in hospital and postanaesthesia care unit (PACU) were compared between dexamethasone groups using weighted and unweighted linear regression models for the logarithm of length of stay, with hospital length of stay truncated at 30 days and PACU length of stay truncated at 12 h. Patients who died before hospital discharge were assigned the longest length of stay. All analyses were conducted using Stata version 12.1 (Stata Corporation, College Station, TX, USA). All *P*-values were two-sided, and a *P*-value <0.05 was considered statistically significant.

Results

Between May 30, 2008 and September 28, 2013, 7112 subjects were enrolled and randomized in 45 participating centres from 10 countries, and 5499 were included in this analysis (Fig. 1). Of the 6992 subjects in whom the primary outcome was assessed, we excluded 1454 subjects from four countries because of the low numbers of subjects treated with dexamethasone in these countries (violation of the positivity assumption). A total of 41 of these 1454 subjects were treated with dexamethasone. A further 12 subjects were excluded from the propensity score model because of missing values of one or more variables, including two subjects with missing dexamethasone use and one with missing prophylactic antibiotic data. An additional 27 subjects were excluded to ensure satisfaction of the 'common support' condition.

Dexamethasone was administered to 2178 (40%) of the 5499 subjects included in this analysis. Subjects who received dexamethasone were younger and were more likely to be female, non-smokers with a higher PONV risk score, and were less likely to have diabetes mellitus or an infection or fever at the time of surgery (Table 1). They were also more likely to receive nitrous oxide and experienced longer surgical times. Weighting by the inverse of the propensity score eliminated these imbalances to produce high levels of balance for these variables between the dexamethasone use groups (Table 1). Dexamethasone had no effect on the risk of wound infection [189 (8.7%) *vs* 275 (8.3%); propensity score-adjusted RR 1.10; 95% CI 0.89–1.34; $P=0.38$] or severe PONV on day 1 [242 (7.3%) *vs* 189 (8.7%); propensity score-adjusted RR 1.06; 95% CI 0.86–1.30; $P=0.59$; Table 2]. Subgroup analyses of dexamethasone use and diabetic status and the contamination status of the surgical wound indicated that there was no difference in the risk of wound infection in these subgroups ($P=0.43$ and $P=0.91$, respectively; Table 3). Dexamethasone also had no effect upon the QoR score on day 1 [propensity score-adjusted median 14, interquartile range (IQR) 12–15, *vs* propensity score-adjusted median 14, IQR 12–16, $P=0.10$], length of stay in PACU [propensity score-adjusted median (IQR) 2.0 (1.3, 2.9) *vs* 1.9 (1.3, 3.1), $P=0.60$], or the primary composite outcome [159 (7.3%) *vs* 333 (10%); propensity score-adjusted RR 0.84; 95% CI 0.69–1.03; $P=0.090$]. Dexamethasone administration was associated with a decrease in the risk of fever on days 1–3 [182 (8.4%) *vs* 488 (14.7%); propensity score-adjusted RR 0.61; 95% CI 0.5–0.74; $P<0.0001$] and shorter lengths of stay in hospital [propensity score-adjusted median (IQR) 5.0 (2.9, 8.2) *vs* 5.3 (3.1, 9.1), $P<0.001$; Table 4]. Discharge from hospital in the dexamethasone group occurred, on average, 1

Table 1 Baseline subject characteristics (n=5499). *Except for age, BMI, pre-induction heart rate, and duration of surgery, which are presented as mean (SD); surgery duration is also presented as the median (IQR). †χ^2 test (categorical variables) or analysis of variance (continuous variables), unweighted or weighted as appropriate; for surgery duration represented as median (IQR), the P-values are based on weighted and unweighted linear regression models for the logarithm of surgery duration. ‡Apfel risk score (1–4). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; COX, cyclooxygenase; ENT, ear nose and throat; IQR, interquartile range; LMWH, low molecular weight heparin; METS, metabolic equivalents; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; PCI, percutaneous coronary intervention; PONV, postoperative nausea and vomiting; PVD, peripheral vascular disease; Std diff., standardized difference; TIA, transient ischaemic attack

Characteristic	Unweighted				Propensity score weighted			
	No dexamethasone [% (n)]* (n=3321)	Dexamethasone [% (n)]* (n=2178)	Std diff. (%)	P-value†	No dexamethasone (%)	Dexamethasone (%)	Std diff. (%)	P-value†
Male	68.7 (2280)	58.7 (1279)	20.76	<0.001	64.7	64.4	0.49	0.877
Exercise capacity ≥4 METS	73.1 (2426)	75.5 (1644)	−5.56	0.044	74.1	74.5	−0.80	0.803
Hypertension	84.3 (2801)	83.7 (1823)	1.75	0.525	83.7	83.9	−0.42	0.892
Coronary artery disease	42.3 (1405)	38.8 (846)	7.06	0.011	40.6	40.5	0.13	0.968
Heart failure	8.4 (279)	6.3 (137)	8.10	0.004	7.6	7.6	0.27	0.939
Previous MI	25.8 (857)	23.8 (518)	4.68	0.090	24.7	24.1	1.33	0.673
Previous CABG/PCI	26.4 (876)	25.8 (561)	1.41	0.609	25.9	25.8	0.21	0.948
PVD	42.3 (1404)	32.6 (709)	20.20	<0.001	38.5	38.3	0.33	0.918
Previous stroke/TIA	17.7 (589)	18.6 (406)	−2.35	0.394	18.0	18.2	−0.46	0.884
High cholesterol	58.4 (1939)	58.7 (1279)	−0.69	0.804	58.6	58.5	0.25	0.936
Current smoker	22.5 (747)	17.9 (390)	11.44	<0.001	20.6	20.6	0.09	0.977
Asthma/COPD	19.6 (650)	20.7 (450)	−2.72	0.324	19.9	19.9	−0.04	0.989
Diabetes mellitus	39.4 (1309)	26.5 (577)	27.76	<0.001	34.8	36.0	−2.77	0.414
Infection/fever	5.4 (179)	2.1 (46)	17.32	<0.001	4.2	4.3	−0.70	0.865
Vegan/vegetarian	1.4 (48)	1.9 (42)	−3.75	0.167	1.6	1.9	−2.30	0.490
Folate/multivitamin	21.5 (713)	17.2 (374)	10.90	<0.001	19.7	19.6	0.16	0.960
Vitamin B_{12} injection	3.2 (107)	3.1 (67)	0.83	0.763	3.1	2.9	1.18	0.674
Aspirin in last 5 days	46.0 (1529)	43.8 (954)	4.50	0.103	45.0	44.3	1.57	0.619
Other NSAID in last 2 days	4.5 (148)	4.8 (105)	−1.73	0.528	4.8	5.0	−1.04	0.764
Clopidogrel in last 7 days	6.7 (223)	5.4 (117)	5.64	0.043	6.3	6.4	−0.35	0.920
Warfarin in last 7 days	5.8 (191)	5.1 (112)	2.68	0.333	5.6	5.3	0.97	0.759
COX2 inhibitor	2.7 (90)	3.9 (85)	−6.67	0.014	3.2	3.4	−0.99	0.752
Nitrates	9.8 (325)	9.2 (201)	1.90	0.492	9.5	9.6	−0.31	0.925
Statins	69.3 (2302)	72.5 (1578)	−6.91	0.013	70.7	70.4	0.86	0.790
ACEI/ARB	58.4 (1939)	61.1 (1331)	−5.56	0.044	59.0	58.4	1.36	0.672
Amiodarone	1.5 (50)	1.4 (31)	0.68	0.804	1.4	1.2	1.36	0.600
β-Blockers	40.4 (1343)	35.3 (768)	10.69	<0.001	38.7	38.8	−0.37	0.909
Heparin/LMWH	9.3 (308)	6.9 (150)	8.77	0.002	8.6	8.3	0.97	0.771
Diuretics	26.8 (891)	23.3 (508)	8.09	0.004	25.4	25.7	−0.58	0.861
CCB	31.5 (1047)	30.1 (656)	3.05	0.270	31.3	32.3	−2.15	0.515
Digoxin	4.0 (133)	2.7 (58)	7.48	0.008	3.5	3.5	0.02	0.995
Insulin	13.1 (435)	6.3 (138)	22.98	<0.001	10.6	10.7	−0.18	0.962
Oral hypoglycaemic	26.9 (894)	18.9 (412)	19.13	<0.001	24.1	24.9	−1.79	0.602
Cardiac perfusion scan	13.6 (453)	11.7 (254)	5.95	0.032	12.8	12.4	1.19	0.702
Surgery cleanliness	92.1 (3057)	91.1 (1984)	3.45	0.209	91.4	90.9	1.86	0.581
Nitrous oxide free	51.7 (1717)	47.6 (1037)	8.18	0.003	50.1	50.4	−0.56	0.859
Prophylactic antibiotics	94.5 (3139)	95.5 (2080)	−4.51	0.106	94.8	94.7	0.43	0.934
Serotonin antagonist	42.2 (1403)	49.6 (1081)	−14.86	<0.001	55.3	55.0	0.61	0.846
Antidopaminergic	3.5 (117)	5.8 (126)	−10.75	<0.001	95.1	95.6	−1.99	0.522
Other antiemetic	2.6 (85)	3.0 (65)	−2.59	0.344	97.1	97.1	−0.29	0.930
Country				<0.001				0.94
1	38.8 (1287)	25.5 (555)	28.71		33.9	35.1	−2.75	
44	2.7 (91)	2.1 (46)	4.08		2.5	2.3	1.18	
60	6.8 (227)	2.0 (43)	23.86		4.9	4.8	0.61	
61	42.5 (1413)	55.8 (1215)	−26.71		47.2	46.7	1.09	
64	9.1 (303)	14.6 (319)	−17.13		11.6	11.2	1.32	

(continued)

Table 1 (continued)

Characteristic	Unweighted				Propensity score weighted			
	No dexamethasone [% (*n*)]* (*n*=3321)	Dexamethasone [% (*n*)]* (*n*=2178)	Std diff. (%)	*P*-value†	No dexamethasone (%)	Dexamethasone (%)	Std diff. (%)	*P*-value†
Race				<0.001				0.984
White	85.8 (2850)	92.6 (2017)	−22.02		88.2	88.3	−0.09	
Asian	6.5 (217)	2.4 (52)	20.19		4.9	5.1	−1.01	
Indian/Pakistan	2.3 (75)	1.8 (39)	3.32		2.2	2.0	1.70	
Hispanic	0.5 (16)	0.5 (10)	0.33		0.5	0.5	−0.17	
Black	2.0 (65)	0.8 (17)	10.14		1.5	1.4	1.04	
Other	3.0 (98)	2.0 (43)	6.30		2.7	2.8	−0.73	
ASA				<0.001				0.925
I	0.3 (11)	0.3 (7)	0.17		0.3	0.2	1.24	
II	21.3 (706)	27.0 (589)	−13.55		23.7	23.7	−0.01	
III	68.4 (2271)	66.7 (1452)	3.67		67.6	67.9	−0.79	
IV–V	10.0 (333)	6.0 (130)	15.00		8.4	8.1	1.13	
Intraoperative PONV score‡				<0.001				0.984
0	9.5 (314)	6.0 (130)	13.10		8.0	8.1	−0.38	
1	43.1 (1432)	30.7 (669)	25.92		38.6	39.1	−1.01	
2	37.5 (1244)	45.6 (993)	−16.56		40.1	40.0	0.11	
3	9.7 (323)	17.4 (378)	−22.44		13.0	12.4	1.79	
4	0.2 (8)	0.4 (8)	−2.30		0.3	0.4	−1.40	
Surgery type				<0.001				0.994
Urology/kidney	8.1 (268)	7.7 (168)	1.32		7.8	7.5	1.16	
Neurology/spine	6.0 (200)	12.9 (282)	−23.80		8.6	8.5	0.35	
Gastrointestinal	6.5 (217)	6.0 (130)	2.34		6.5	6.7	−0.92	
Liver/pancreas	4.8 (159)	4.5 (97)	1.59		4.9	5.5	−3.02	
ENT	2.5 (83)	3.8 (83)	−7.51		3.1	3.2	−0.47	
Orthopaedic	13.0 (432)	13.9 (303)	−2.65		13.0	13.3	−0.91	
Plastics	1.0 (33)	2.3 (50)	−10.25		1.8	1.6	2.13	
Gynaecological	2.9 (96)	5.2 (114)	−11.89		3.8	4.0	−1.29	
Other	2.1 (70)	2.5 (54)	−2.48		2.4	2.5	−0.93	
Vascular	50.5 (1678)	38.3 (835)	24.72		45.4	44.4	2.14	
Colorectal	2.6 (85)	2.8 (62)	−1.77		2.7	2.8	−0.61	
Age (yr)	69.4 (9.8)	68.9 (9.6)	4.9	0.075	69.1 (11.0)	69.1 (8.4)	−0.08	0.980
BMI (kg m^{-2})	28.4 (6.3)	29.0 (6.5)	−9.7	<0.001	28.7 (7.0)	28.6 (5.8)	0.10	0.976
Pre-induction heart rate (beats min^{-1})	72.4 (14.2)	72.6 (14.1)	−1.3	0.628	72.5 (15.5)	72.5 (12.5)	0.06	0.985
Duration of surgery (h)								
Mean (SD)	2.9 (1.6)	2.8 (1.5)	5.8	0.038	2.9 (1.8)	2.9 (1.4)	1.38	0.672
Median (IQR)	2.6 (1.9, 3.6)	2.5 (1.8, 3.4)		0.079	2.5 (1.8, 3.6)	2.5 (1.8, 3.5)		0.871

day earlier. Results were broadly similar when inverse probability of treatment weights were not adjusted for and when these weights were truncated at the 99th percentile.

Discussion

In this *post hoc* subgroup analysis, wound infection within 30 days of surgery occurred in 464 of the 5499 (8.4%) included subjects. This is similar to the rate observed in the total trial cohort (632, 9%) and consistent with reported rates in comparable populations.[13] The results of this analysis indicate that the administration of dexamethasone was not associated with an increase in the risk of wound infection, had no effect on the day 1 QoR score, and had no effect on the length of stay in the PACU. However, dexamethasone administration was associated with a decrease in the risk of fever and expedited hospital discharge. Neither diabetes mellitus nor the contamination status of the surgical wound altered the risk of wound infection. Dexamethasone was not associated with an increased risk of the primary composite end point of the main trial. Given that antiemetic doses of dexamethasone are frequently administered to surgical patients, these findings imply the safety of dexamethasone, but must be interpreted in the context of the known weaknesses of this analysis discussed below.

Our results do not suggest an association between dexamethasone administration and the incidence of surgical site infection. We did not identify any influence of diabetes mellitus or surgical wound contamination status on wound infection rates, two factors that have been previously associated with increased postoperative infection risk.[14 15] Postoperative infections, particularly wound infections, are important because they prolong hospital stay, increase costs, and have an impact

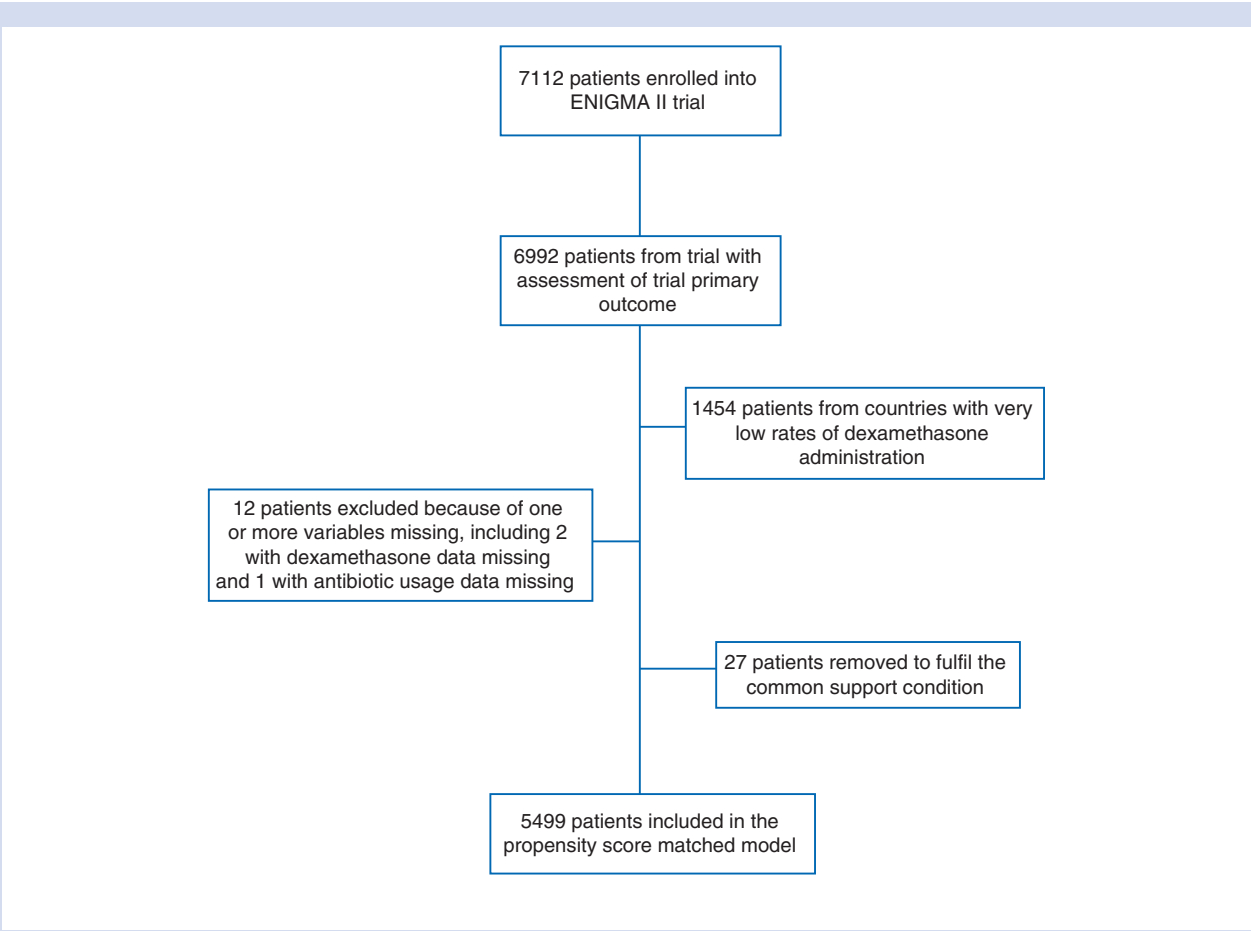

Fig 1. CONSORT diagram of trial processes.

Table 2 Estimated associations with outcomes for dexamethasone, including diabetes and surgery cleanliness subgroup interactions. *Wald test *P*-value from unweighted or weighted binary regressions. Wound infection is a purulent discharge, with positive culture, as documented. CI, confidence interval; PONV, postoperative nausea and vomiting; RR, relative risk

	No dexamethasone [*n* (%)] (*n*=3321)	Dexamethasone [*n* (%)] (*n*=2178)	Unadjusted		Propensity score adjusted		Propensity score adjusted (truncated at the 99th percentile)	
			RR (95% CI)	*P*-value*	RR (95% CI)	Pvalue*	RR (95% CI)	*P*-value*
Wound infection	275 (8.3)	189 (8.7)	1.05 (0.88–1.25)	0.60	1.10 (0.89–1.34)	0.376	1.08 (0.89–1.31)	0.440
Composite end point	333 (10.0)	159 (7.3)	0.73 (0.61–0.87)	0.001	0.84 (0.69–1.03)	0.090	0.86 (0.70–1.05)	0.130
Severe PONV day 1	242 (7.3)	189 (8.7)	1.19 (0.99–1.43)	0.060	1.06 (0.86–1.30)	0.589	1.06 (0.86–1.29)	0.588
Fever any of days 1–3	488 (14.7)	182 (8.4)	0.57 (0.48–0.67)	<0.001	0.61 (0.50–0.74)	<0.001	0.60 (0.50–0.72)	<0.001

on postoperative mortality that extends at least to 30 days.[16] Potential mechanisms by which dexamethasone might increase perioperative infection include immunosuppressive effects[17] and hyperglycaemia.[6] A large randomized trial in cardiac surgery patients has reported a 4.9% absolute reduction in the risk of postoperative infection in patients receiving dexamethasone 1 mg kg^{-1}, primarily related to the incidence of postoperative pneumonia.[18] However, comparable large randomized controlled trials to evaluate the effect of intraoperative dexamethasone, at commonly administered doses (4–8 mg), on postoperative infections in non-cardiac surgical patients are lacking. A *post hoc* analysis of the PROXI trial did not identify an association between dexamethasone and either wound complications (infection or dehiscence) or mortality.[19] A retrospective case–control study suggested that dexamethasone increases infection risk,[20] but a retrospective cohort study did not confirm

Table 3 Relative risks for wound infection associated with the use of dexamethasone in subgroups. *Interaction P-value based on the Wald test. CI, confidence interval; RR, relative risk

	No dexamethasone [n (%)] (n=3321)	Dexamethasone [n (%)] (n=2178)	Unadjusted		Propensity score adjusted		Propensity score adjusted (truncated at the 99th percentile)	
			RR (95% CI)	P-value*	RR (95% CI)	P-value*	RR (95% CI)	P-value*
Diabetes mellitus				0.886		0.434		0.488
Yes	124 (3.7)	58 (2.7)	1.06 (0.79–1.43)		1.20 (0.86–1.69)		1.18 (0.85–1.62)	
No	151 (4.5)	131 (6.0)	1.09 (0.87–1.36)		1.02 (0.80–1.30)		1.02 (0.80–1.30)	
Wound contamination				0.796		0.907		0.669
Clean	239 (7.2)	163 (7.5)	1.05 (0.87–1.27)		1.10 (0.88–1.36)		1.20 (0.89–1.35)	
Dirty	36 (1.1)	26 (1.2)	0.98 (0.61–1.57)		1.06 (0.60–1.86)		0.97 (0.58– 1.63)	

Table 4 Median (interquartile range) of length of stay in hospital and postanaesthesia care unit, by use of dexamethasone. *P-value from unweighted/weighted regression models for the logarithm of length of stay. IQR, interquartile range; PACU, postanaesthesia care unit

	Unadjusted			Propensity score adjusted			Propensity score adjusted (truncated at the 99th percentile)		
	Dexamethasone [median (IQR)]	No dexamethasone [median (IQR)]	P-value*	Dexamethasone [median (IQR)]	No dexamethasone [median (IQR)]	P-value*	Dexamethasone [median (IQR)]	No dexamethasone [median (IQR)]	P-value*
Discharge from hospital	5.0 (3.0, 8.0)	5.6 (3.1, 9.3)	<0.001	5.0 (2.9, 8.2)	5.3 (3.1, 9.1)	<0.001	5.0 (2.9, 8.2)	5.3 (3.1, 9.1)	<0.001
Discharge from PACU	1.8 (1.3, 2.7)	2.0 (1.3, 3.2)	<0.001	2.0 (1.3, 2.9)	1.9 (1.3, 3.1)	0.60	1.9 (1.3, 2.9)	1.9 (1.3, 3.1)	0.53

these findings.[21] Two small randomized trials also failed to demonstrate an association between dexamethasone and infection.[13 22] One was prematurely terminated, and both were underpowered.[23] Although meta-analyses of small and moderate-sized trials examining antiemetic or analgesic effects of dexamethasone have not identified increased risks of postoperative infection, most studies did not evaluate infection prospectively.[24 25] Published meta-analyses and practice guidelines have asserted the apparent safety of perioperative glucocorticoids in general, and dexamethasone in particular, in terms of infection risk,[2 26 27] but loose or absent definitions of adverse outcomes in published trials and the absence of systematic postoperative surveillance have provoked much discussion.[5 28] There is therefore inconsistency in the literature and a need for clarity around risks associated with dexamethasone administration to surgical patients.

Dexamethasone has been demonstrated in multiple trials to have powerful and long-lasting antiemetic effects,[2 25 29] but our analysis did not identify a decrease in the incidence of severe PONV (on day 1). This finding is consistent with what has been published from a previous subgroup analysis from this data set[30] (Appendix). There is no universal definition of PONV; it is most usually defined as a single episode of nausea or vomiting in the 24–48 h after surgery.[29 31] Many such incidents are minor and transient and of questionable clinical importance. However, persistent or recurrent PONV is both unpleasant and has distinct clinical importance for patients.[32 33] Hence, for this trial, only severe PONV (two or more episodes of nausea, expulsion of gastric contents, or both at least 6 h apart, or requiring treatment with at least three doses of at least two different classes of antiemetic medication in any 24 h period during the 3 days after surgery) was considered as PONV. Severe PONV, so defined, is associated with lower recovery scores and protracted hospitalization.[30] It may be that the lack of an observed effect of dexamethasone on day 1 is attributable to the use of a different metric for PONV than has been used previously in trials that support an antiemetic action of dexamethasone.

In this analysis, dexamethasone did not influence the primary outcome (death and composite cardiovascular outcomes at 30 days after surgery). This is not surprising, because there does not appear to be a plausible biological mechanism for such an effect. Dexamethasone has numerous properties that make it an attractive agent to use in surgical patients. It improves analgesia, prolongs the duration of the analgesia of regional anaesthesia blocks, and can improve the quality of recovery, facilitating earlier hospital discharge.[34–36] It can decrease

sore throat in intubated patients[37 38] and swelling in dental and maxillofacial surgery[39] and has well-documented antiemetic efficacy.[25] An improvement in these outcomes would be expected to influence the QoR score and time to PACU discharge, but we did not demonstrate an effect on either parameter. Conversely, the time to hospital discharge was shorter in the dexamethasone group, and although this is often quoted as a surrogate of general care, recovery from surgery is a complex construct.[40] Hence, the reasons to account for these findings are not immediately evident from this analysis. The suppression of fever on days 1–3 is consistent with the well-known anti-inflammatory effects of dexamethasone.[13 18 41]

Although this analysis has many strengths, it shares the recognized weaknesses of the analysis of non-randomized interventions.[42] Despite the development of a propensity score model, there are likely to be unmeasured and unknown factors contributing to residual confounding of the relationships between dexamethasone and outcomes. The original trial was not designed to examine the influence of dexamethasone on infection risk. Dexamethasone administration was at the discretion of the anaesthetist, who was not blinded to whether the patients received nitrous oxide or not and may have been influenced by knowledge of its emetogenic potential. An explanation for the failure to identify an antiemetic effect is that because the administration of antiemetic prophylaxis was not randomized, propensity-based methods might not account fully for such residual confounding influencing the patterns of dexamethasone administration. Furthermore, we did not collect the dose of dexamethasone administered. Hence, a lower dose of 4 mg might have been used rather than the higher acceptable dose[2] of 8 mg, reducing less severe PONV but leaving the incidence of severe PONV unchanged. Although postoperative surveillance for wound infections did occur up to day 30, this relied largely upon patient self-reporting, which has been shown to miss up to 10.5% of postoperative wound infections.[43] Hence, it is likely that we may have underestimated the true infection rates. Furthermore, the ethnicity of >90% of our study subjects was classified as 'white', and our conclusions can therefore be applied only to this population.

Strengths of this substudy are multiple. Our analysis was derived from a large, international, multicentre trial that used validated and objective outcome definitions and data collection methods. We included 5499 subjects for the subgroup analysis, with complete follow-up in 99.9%. The propensity score-weighted analysis successfully corrected the large standardized differences, indicating its efficacy, and included factors known to influence the decision to administer dexamethasone as an antiemetic.[1]

In conclusion, this subgroup analysis of data from a large multicentre randomized controlled trial has not identified an association between the administration of dexamethasone as an antiemetic to high-risk non-cardiac surgical patients and the rates of postoperative wound infections. Our findings are consistent with the currently available safety data in relationship to the absence of an infection risk and the administration of dexamethasone in the perioperative period.[2 5 26 29] Nonetheless, meta-analyses and *post hoc* subgroup analyses have weaknesses, and they do not obviate the need for high-quality adequately powered randomized trials.[42] Dexamethasone is administered to large numbers of surgical patients worldwide every year, and the implications of even a small increase in wound infection would be very large. The currently recruiting 'Perioperative ADministration of Dexamethasone and Infection (PADDI)' trial (ACTRN12614001226695) is designed to provide a definitive answer to questions of infection-related safety of dexamethasone, but until the results become available, concerns relating to wound infection risk in surgical patients should not be an impediment to the considered administration of dexamethasone.

Authors' contributions

Design of the original study and composition of the study protocol: M.T.V.C., K.L., M.P., A.F., P.M.
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Design of the substudy: T.C., J.K., T.G.S., E.O'L., P.M.
Design of the statistical analysis plan: A.F.
Data analysis: T.C., J.K., T.G.S., E.O'L., P.M.
Writing of the manuscript: T.C., J.K., T.G.S., E.O'L., M.T.V.C., K.L., M.P., A.F., P.M.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Declaration of interest

T.C. is a member of the executive committee of the ANZCA Clinical Trials Network (ANZCA CTN). He is supported by a Raine Foundation Clinical Practitioner Fellowship, Health Department of Western Australia, and the University of Western Australia. T.G.S. and K.L. are members of the executive committee of the ANZCA Clinical Trials Network (ANZCA CTN). M.T.V.C. is a member of the executive committee of the ANZCA Clinical Trials Network (ANZCA CTN) and an editorial board member of the *BJA*. M.P. is an editor of *Anaesthesia and Intensive Care*; and on the editorial boards of *International Journal of Obstetric Anesthesia*, *Obstetric Anesthesia Digest*, and *Anesthesiology and Pain Medicine*. P.M. is a member of the executive committee of the ANZCA Clinical Trials Network (ANZCA CTN) and is an editor of the *BJA*. J.K., E.O'L. and A.F. have no interests to declare.

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Appendix

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