ORIGINAL ARTICLE

Dexamethasone and Surgical-Site Infection

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ABSTRACT

BACKGROUND

The glucocorticoid dexamethasone prevents nausea and vomiting after surgery, but there is concern that it may increase the risk of surgical-site infection.

METHODS

In this pragmatic, international, noninferiority trial, we randomly assigned 8880 adult patients who were undergoing nonurgent, noncardiac surgery of at least 2 hours' duration, with a skin incision length longer than 5 cm and a postoperative overnight hospital stay, to receive 8 mg of intravenous dexamethasone or matching placebo while under anesthesia. Randomization was stratified according to diabetes status and trial center. The primary outcome was surgical-site infection within 30 days after surgery. The prespecified noninferiority margin was 2.0 percentage points.

RESULTS

A total of 8725 participants were included in the modified intention-to-treat population (4372 in the dexamethasone group and 4353 in the placebo group), of whom 13.2% (576 in the dexamethasone group and 572 in the placebo group) had diabetes mellitus. Of the 8678 patients included in the primary analysis, surgical-site infection occurred in 8.1% (354 of 4350 patients) assigned to dexamethasone and in 9.1% (394 of 4328) assigned to placebo (risk difference adjusted for diabetes status, −0.9 percentage points; 95.6% confidence interval [CI], −2.1 to 0.3; P<0.001 for noninferiority). The results for superficial, deep, and organ-space surgical-site infections and in patients with diabetes were similar to those of the primary analysis. Postoperative nausea and vomiting in the first 24 hours after surgery occurred in 42.2% of patients in the dexamethasone group and in 53.9% in the placebo group (risk ratio, 0.78; 95% CI, 0.75 to 0.82). Hyperglycemic events in patients without diabetes occurred in 22 of 3787 (0.6%) in the dexamethasone group and in 6 of 3776 (0.2%) in the placebo group.

CONCLUSIONS

Dexamethasone was noninferior to placebo with respect to the incidence of surgical-site infection within 30 days after nonurgent, noncardiac surgery. (Funded by the Australian National Health and Medical Research Council and others; PADDI Australian New Zealand Clinical Trials Registry number, ACTRN12614001226695.)

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N Engl J Med 2021;384:1731-41.
DOI: 10.1056/NEJMoa2028982

Postoperative nausea and vomiting are major challenges in perioperative care and occur in 25 to 30% of all patients who undergo surgery and in up to 80% of patients in high-risk populations.[1] Dexamethasone is an inexpensive, effective, long-acting agent for the prophylaxis and treatment of postoperative nausea and vomiting[1,2] and is administered to more than 50% of patients who undergo surgery with general anesthesia.[3] However, the drug has rapid and extensive effects on immune function.[4,5] Therefore, there has been concern that dexamethasone may increase the risk of postoperative infection, particularly in vulnerable populations such as patients with diabetes.[6-8] Surgical-site infections are common complications after surgery and are associated with increased mortality and excess health expenditure,[9] estimated at $10 billion annually in the United States.[10] We conducted the Perioperative Administration of Dexamethasone and Infection (PADDI) trial to assess the effects of dexamethasone on the risk of surgical-site infections in adults undergoing nonurgent, noncardiac surgery.

Methods

Trial Design

In this pragmatic, international, multicenter, randomized, placebo-controlled, triple-blind (patient, anesthesiologist, and assessor), noninferiority trial, patients were assigned to receive 8 mg of intravenous dexamethasone or matching placebo after induction of general anesthesia and before surgical incision. The rationale and design of the trial have been reported previously.[11] The trial and the protocol (available with the full text of this article at NEJM.org) were approved by the institutional review board at each participating site.

Patient Selection and Randomization

Eligible adult patients had an American Society of Anesthesiologists (ASA) physical status classification of I to IV (on a scale of I to VI, with higher classes indicating more severe systemic disease) and were undergoing elective or expedited nonurgent, noncardiac surgery with general anesthesia and an expected operative duration of at least 2 hours as well as an expected postoperative hospital stay of at least 1 night. Patients were excluded if they were undergoing surgery that was time critical, that involved an expected total incision length of 5 cm or shorter, that was associated with a primary infection (e.g., infection related to a prosthesis), or that required the use of intraoperative dexamethasone. Patients were also excluded if they had poorly controlled diabetes mellitus (defined as a glycated hemoglobin level of >9.0%). Eligible patients were randomly assigned in a 1:1 ratio by means of a Web-based service to receive dexamethasone or placebo in random permuted blocks of size 6 and 12, stratified according to trial center and a diagnosis of diabetes mellitus.

Trial Procedures

Dexamethasone or placebo (supplied in a 2-ml vial and labeled with a randomization letter) was administered as an intravenous bolus within 5 minutes after induction of anesthesia by the attending anesthesiologist. All other aspects of patient care (including prophylactic antibiotic agents, management of blood glucose levels, and medication for patients with diabetes) followed local protocols and established guidelines. Nontrial glucocorticoids were prohibited for up to 30 days after the index surgical procedure.

The primary outcome was assessed in the modified intention-to-treat, per-protocol, and as-treated populations. The primary analysis was performed in the modified intention-to-treat population, which excluded patients who did not undergo eligible surgery (i.e., surgery with a total incision length of >5 cm when the patient was under general anesthesia), who withdrew consent or whose clinician withdrew the patient from the trial, who could not receive dexamethasone or placebo because they were not available at the center, or who met other exclusion criteria. The per-protocol population included the same criteria as those for the modified intention-to-treat population and further excluded patients who did not receive dexamethasone or placebo or who received open-label dexamethasone (or other glucocorticoid) either intraoperatively or within 30 days postoperatively. All secondary and tertiary outcomes were assessed in the modified intention-to-treat population only.

Blinding, Data Quality, and Safety

The members of the clinical end-point committee, who were unaware of trial-group assignments, adjudicated all primary-outcome events.

A list of committee members and details regarding the monitoring of data quality and site audits are provided in the Supplementary Appendix, available at NEJM.org. Two interim analyses were conducted (after 3379 and 5380 patients had been enrolled) by the independent data and safety monitoring committee, and the trial proceeded to completion.

ETHICS, GOVERNANCE, AND FUNDING

Written informed consent was obtained from all participants. Alfred Health oversaw the trial. The members of the steering committee designed the trial, gathered and analyzed the data, and vouch for the accuracy and completeness of the data and adherence of the trial to the protocol. The writing committee wrote the first draft of the manuscript, and the authors, some of whom were members of the steering committee, prepared the manuscript and made the decision to submit it for publication. There was no commercial involvement in the trial. The statistical analysis plan is available with the protocol at NEJM.org.

OUTCOMES

The primary outcome was the occurrence of a surgical-site infection within 30 days after surgery, determined according to the Centers for Disease Control and Prevention definitions, which comprise three categories: superficial incisional, deep incisional, and organ-space infection (Tables S1 and S2 in the Supplementary Appendix).[12] Secondary outcomes included superficial, deep, and organ-space infections within 30 days after surgery, assessed separately; deep and organ-space infections within 90 days after surgery in patients who had insertion of prosthetic material, considered separately; other infections (including urinary tract infections, pneumonia, catheter-related infections, and sepsis) within 30 days after the index procedure; the quality of recovery (as assessed with the use of the 15-item quality-of-recovery [QoR-15] scale, with scores ranging from 0 to 150 and higher scores indicating better quality of recovery) on days 1 and 30[13]; chronic postsurgical pain at 6 months after surgery; and death or persistent new-onset disability within 6 months after surgery.[14] Details regarding tertiary outcomes, adverse events, and safety outcomes (including myocardial infarction, cerebrovascular accident, deep venous thrombosis or pulmonary embolism, and other serious adverse events) are provided in the Supplementary Appendix.

Patients were followed in the postanesthesia care unit, on the first 3 postoperative days, at hospital discharge, and at 30 days and 6 months after surgery. Active postoperative surveillance of surgical-site infection involved several processes. A wound assessment was performed on day 3 if the patient was still hospitalized. On day 30 and at 6 months, patients completed a telephone interview for wound assessment, and their medical records were reviewed to identify the occurrence of trial outcomes. Research staff members collated source documentation to enable outcome adjudication. Scores on the QoR-15 scale were assessed on days 1 and 30.[13] Details regarding the outcome adjudication process and assessments (including additional assessments of pain and disability that are not included in this article) are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

A noninferiority margin of 2.0 percentage points was determined with the assistance of clinical experts and was set on the basis of a modified Delphi process and an anticipated incidence of surgical-site infection of 9%.[15] With an expected incidence of infection of 9% in each group, we determined that 4303 patients per group would be needed to give the trial 90% power to detect noninferiority of dexamethasone; noninferiority would be concluded if the upper boundary of the two-sided 95% confidence interval for the difference in infection rates was less than 2.0 percentage points. As prespecified in the trial protocol, two interim analyses were planned — when one third and two thirds of the total number of patients had been enrolled. The analyses would use two-sided repeated asymmetric confidence intervals to preserve an overall confidence level of 95% and would use the O'Brien–Fleming function to determine the upper boundary of the confidence intervals and the power-spending function for the lower boundaries. The 90% power using these confidence intervals was confirmed by means of numerical simulation. Target recruitment was set at 8880 patients to account for a 3% loss to follow-up. An overall 5% significance level was used, and no correction for multiple testing was applied, apart from adjust-

ment for the multiplicity of interim analyses for the primary outcome.

The absolute difference in 30-day infection rates was estimated with the use of binomial regression with an identity-link function, with adjustment for diabetes status; a risk ratio was also calculated using a logarithmic-link function. The analyses used 95.6% asymmetric confidence intervals based on the actual timing of the two interim analyses and spending functions. Noninferiority P values were calculated as one-sided, based on a null hypothesis of inferiority, with a significance level of 2.37% to account for the interim analyses.[16] Sensitivity analyses were performed to account for missing data by imputing outcomes under "worst–best" and "best–worst" case scenarios (Table S10).[17]

Comparisons between groups for secondary and tertiary outcomes were estimated as risk ratios (for binary outcomes), differences in medians (for continuous outcomes), and hazard ratios (for time-to-event outcomes). Information regarding all statistical analyses is provided in the statistical analysis plan.

Planned subgroup analyses for the primary outcome were assessed with the use of regression models with terms for the interactions between the subgroup and randomized group and between the subgroup and diabetes status. Results are reported with 95.6% confidence intervals for each subgroup, accounting for the interim analyses. The subgroups were defined on the basis of diabetes status, sex, risk of infection, age quintile, and country of enrollment. Exploratory analyses in additional prespecified subgroups were body-mass index, ASA physical status classification, wound classification (clean or contaminated), smoking status, average intraoperative fraction of inspired oxygen during anesthesia (quintile), and duration of surgery (quintile).

RESULTS

PATIENT ENROLLMENT AND FOLLOW-UP

Recruitment began on March 10, 2016; the last patient underwent randomization on July 29, 2019, and the final follow-up was completed on February 26, 2020. Of the 26,909 patients who met eligibility requirements, 8880 agreed to participate and underwent randomization. A total of 4444 patients were assigned to receive dexamethasone and 4436 to receive placebo. Of these patients, 8725 (98.3%) met the criteria for inclusion in the modified intention-to-treat population (4372 in the dexamethasone group and 4353 in the placebo group) (Fig. 1). Of these 8725 patients, 1148 (13.2%) had diabetes mellitus, and 1116 (97.2%) had type 2 diabetes (Table 1).

Figure 1 (facing page). Enrollment and Randomization.
The modified intention-to-treat population included patients who had undergone eligible surgery with general anesthesia on the planned date.

The median number of patients per site was 98 (range, 2 to 937). The list of sites and details of their recruitment are provided in Table S3. In the modified intention-to-treat population, 30-day data were available for 8678 of 8725 patients (99.5%). There were no clinically important differences in baseline or intraoperative characteristics between the two groups (Table 1 and Tables S4 through S8). Of the patients in the modified intention-to-treat population with 30-day data, 276 of 4350 patients (6.3%) in the dexamethasone group and 286 of 4328 (6.6%) in the placebo group had protocol deviations (Fig. 1).

PRIMARY OUTCOME

In the modified intention-to-treat population, surgical-site infection within 30 days after surgery occurred in 354 of 4350 patients (8.1%) in the dexamethasone group and in 394 of 4328 (9.1%) in the placebo group (risk difference adjusted for diabetes status, −0.9 percentage points; 95.6% confidence interval [CI], −2.1 to 0.3), a result consistent with noninferiority (risk ratio, 0.89; 95.6% CI, 0.77 to 1.03; P<0.001 for noninferiority) (Table 2). The results of the primary analysis were consistent with noninferiority in the per-protocol population (risk difference, −0.9 percentage points; 95.6% CI, −2.1 to 0.3; P<0.001 for noninferiority) and in the as-treated population (risk difference, 0.04 percentage points; 95.6% CI, −1.2 to 1.2; P=0.001 for noninferiority) (Figs. S1 and S2). These results differed minimally in sensitivity analyses with imputation for missing data and after adjustment for trial site (Tables S10 and S11).

The effect of dexamethasone on the incidence of surgical-site infection was consistent across all prespecified subgroups (Fig. 2). Noninferiority of dexamethasone to placebo was shown in patients with or without diabetes (risk difference

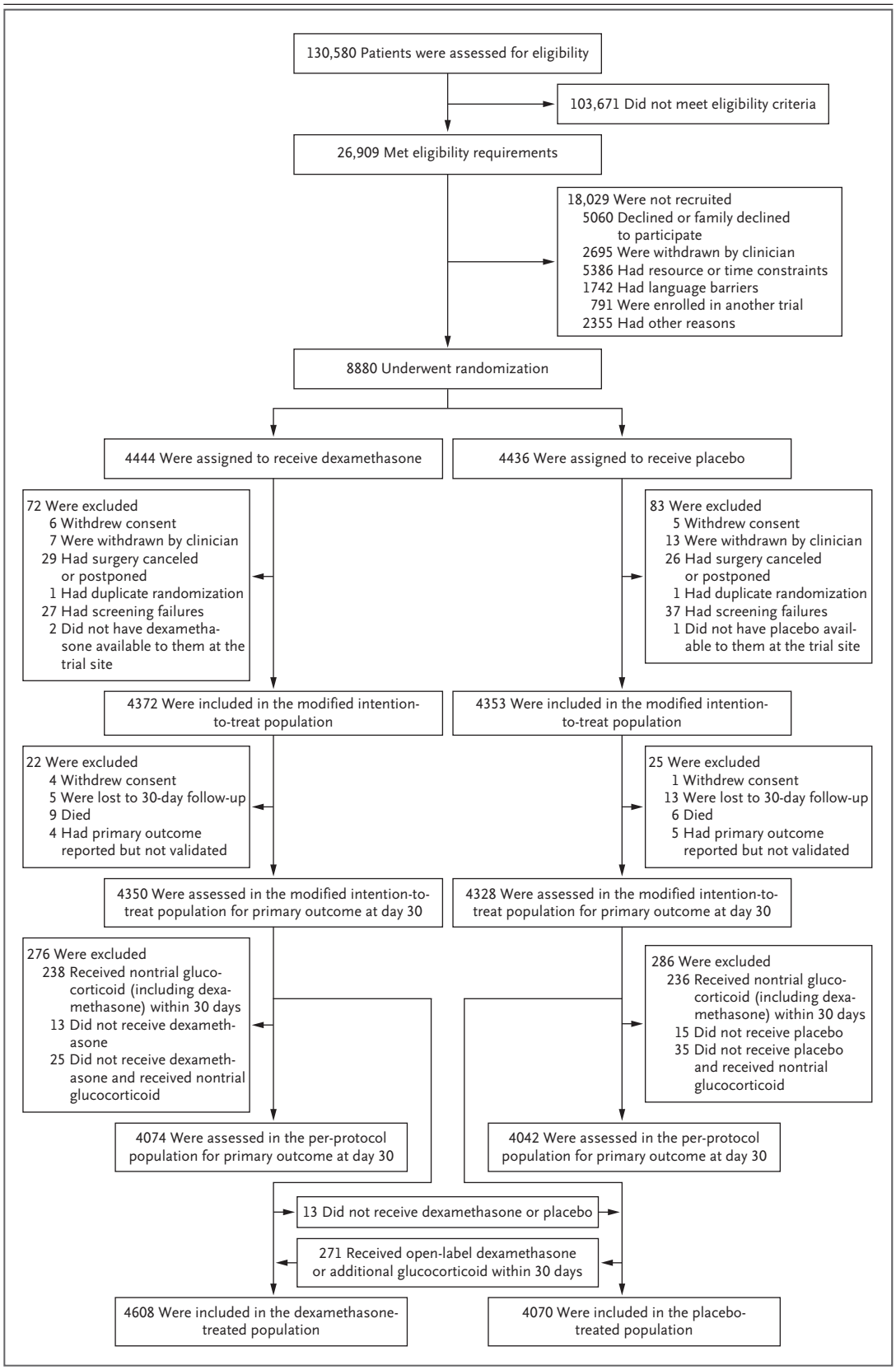


Table 1. Demographic and Preoperative Characteristics in the Modified Intention-to-Treat Population.*

Characteristic	Dexamethasone (N=4372)	Placebo (N=4353)
Age — yr	59.0±14.1	59.3±14.1
Male sex — no. (%)	2398 (54.8)	2381 (54.7)
Body weight — kg	83.2±20.8	83.0±20.5
Body-mass index†	29.0±6.5	29.1±6.5
ASA physical status classification — no./total no. (%)‡		
I	528/4372 (12.1)	532/4352 (12.2)
II	2594/4372 (59.3)	2605/4352 (59.9)
III	1208/4372 (27.6)	1177/4352 (27.0)
IV	42/4372 (1.0)	38/4352 (0.9)
Current smoker — no./total no. (%)	736/4372 (16.8)	716/4352 (16.5)
Diabetes mellitus		
Any form — no./total no. (%)	576/4372 (13.2)	572/4353 (13.1)
Type 1 diabetes	13/576 (2.3)	9/572 (1.6)
Type 2 diabetes	557/576 (96.7)	559/572 (97.7)
Other type	6/576 (1.0)	4/572 (0.7)
Median no. of yr since diagnosis (IQR)	9.0 (4.0–15.0)	8.0 (4.0–14.0)
Daily insulin use — no./total no. (%)	108/576 (18.8)	105/572 (18.4)
Use of oral hypoglycemic agents — no./total no. (%)	449/576 (78.0)	447/572 (78.1)
Use of noninsulin injectable agents — no./total no. (%)	22/576 (3.8)	10/572 (1.7)
Type of surgery — no./total no. (%)		
Ear, nose, throat, or maxillofacial	89/4372 (2.0)	89/4352 (2.0)
Gastrointestinal	983/4372 (22.5)	970/4352 (22.3)
Gynecologic	444/4372 (10.2)	428/4352 (9.8)
Neurosurgery	339/4372 (7.8)	303/4352 (7.0)
Orthopedic	855/4372 (19.6)	857/4352 (19.7)
Plastic surgery	223/4372 (5.1)	212/4352 (4.9)
Urologic	787/4372 (18.0)	829/4352 (19.0)
Vascular	206/4372 (4.7)	221/4352 (5.1)
Other	446/4372 (10.2)	443/4352 (10.2)
Surgical-wound status — no./total no. (%)		
Clean	2950/4372 (67.5)	2937/4351 (67.5)
Clean or contaminated	1397/4372 (32.0)	1380/4351 (31.7)
Contaminated	25/4372 (0.6)	34/4351 (0.8)
Surgical urgency — no./total no. (%)		
Elective	4245/4372 (97.1)	4227/4351 (97.1)
Expedited	127/4372 (2.9)	124/4351 (2.8)
Metal or synthetic material implanted — no./total no. (%)	1439/4372 (32.9)	1395/4351 (32.1)
Use of prophylactic antibiotics — no./total no. (%)	4282/4372 (97.9)	4255/4351 (97.8)
Median duration of surgery (IQR) — hr	2.5 (1.8–3.5)	2.5 (1.8–3.5)
Preoperative laboratory data		
Median glycated hemoglobin level (IQR) — %§		
Patients without diabetes	5.4 (5.2–5.7)	5.4 (5.2–5.7)
Patients with diabetes	6.8 (6.1–7.5)	6.6 (6.1–7.4)

Table 1. (Continued.)

Characteristic	Dexamethasone (N=4372)	Placebo (N=4353)
Median hemoglobin level (IQR) — g/liter	140 (129–150)	140 (130–150)
Median creatinine level (IQR) — μmol/liter	74.0 (64.0–87.0)	74.0 (63.0–87.0)

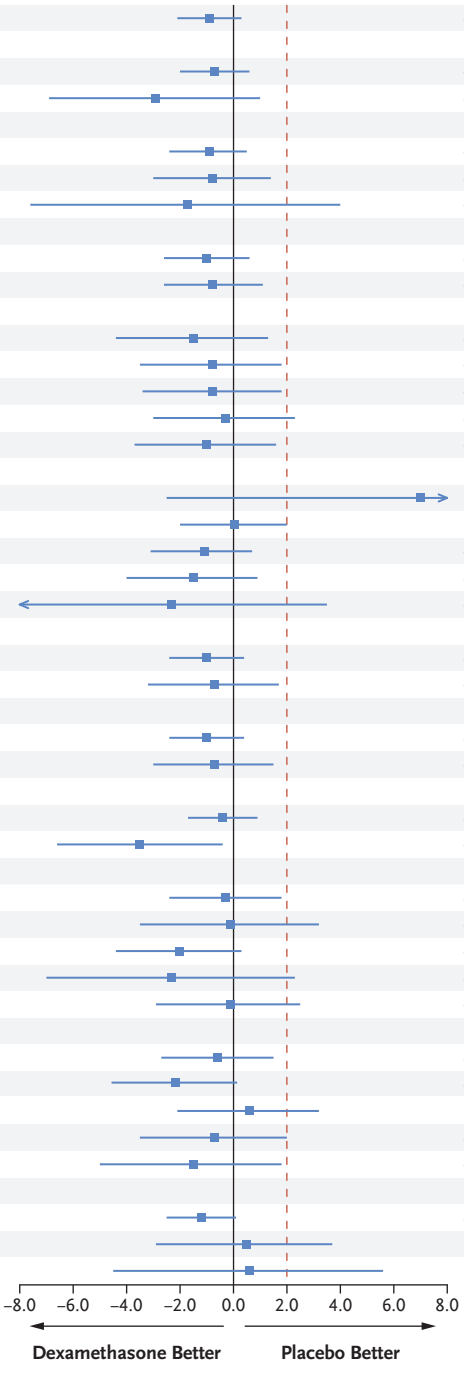
* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. The modified intention-to-treat population included patients who had undergone eligible surgery involving general anesthesia on the planned date. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. IQR denotes interquartile range.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ American Society of Anesthesiologists (ASA) physical status classes range from I to VI, with higher classes indicating more severe systemic disease.
§ Data were missing for 57 patients in the dexamethasone group and 55 patients in the placebo group.

Table 2. Outcomes in the Modified Intention-to-Treat Population.*

Outcome	Dexamethasone (N=4372)	Placebo (N=4353)	Risk Difference, Risk Ratio, or Median Difference (95% CI)
Primary			
Surgical-site infection at 30 days — no./total no. (%)†	354/4350 (8.1)	394/4328 (9.1)	
Risk difference			–0.89 (–2.11 to 0.29)‡
Risk ratio			0.89 (0.77 to 1.03)§
Secondary			
Deep or organ-space surgical-site infection with prosthetic material at 90 days — no./total no. (%)	26/1400 (1.9)	27/1363 (2.0)	0.94 (0.55 to 1.60)¶
Deep surgical-site infection at 90 days	13/1400 (0.9)	16/1363 (1.2)	0.79 (0.38 to 1.64)¶
Organ-space surgical-site infection at 90 days	13/1400 (0.9)	11/1363 (0.8)	1.15 (0.52 to 2.56)¶
Superficial surgical-site infection at 30 days — no./total no. (%)	284/4350 (6.5)	311/4328 (7.2)	0.91 (0.78 to 1.06)¶
Deep surgical-site infection at 30 days — no./total no. (%)	18/4350 (0.4)	16/4328 (0.4)	1.12 (0.57 to 2.19)¶
Organ-space surgical-site infection at 30 days — no./total no. (%)	57/4350 (1.3)	76/4328 (1.8)	0.75 (0.53 to 1.05)¶
Any infection at 30 days — no./total no. (%)	504/4366 (11.5)	544/4348 (12.5)	0.92 (0.82 to 1.03)¶
Urinary tract infection	194/4361 (4.4)	231/4347 (5.3)	0.84 (0.69 to 1.01)¶
Pneumonia	98/4364 (2.2)	94/4348 (2.2)	1.04 (0.79 to 1.38)¶
Infection associated with indwelling catheter	22/4361 (0.5)	13/4347 (0.3)	1.69 (0.85 to 3.34)¶
Sepsis at discharge	38/4370 (0.9)	65/4350 (1.5)	0.58 (0.39 to 0.87)¶
Other	211/4361 (4.8)	218/4347 (5.0)	0.97 (0.80 to 1.16)¶
Median QoR-15 score (IQR)‖			
Day 1	109 (93 to 123)	104 (87 to 118)	5.0 (3.8 to 6.2)**
Day 30	135 (123 to 143)	135 (122 to 144)	0.0 (–0.7 to 0.7)**
New-onset chronic postsurgical pain at 6 mo — no./total no. (%)	371/4254 (8.7)	300/4217 (7.1)	1.23 (1.06 to 1.42)¶
New-onset disability or death at 6 mo — no./total no. (%)	358/4233 (8.5)	338/4158 (8.1)	1.05 (0.90 to 1.21)¶

* Confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. IQR denotes interquartile range.
† The primary outcome was assessed in the modified intention-to-treat population among patients with available 30-day data.
‡ The value is the risk difference reported in percentage points with a 95.6% confidence interval, allowing for multiplicity of interim analyses. P<0.001 for noninferiority.
§ The risk ratio is reported with a 95.6% confidence interval, allowing for multiplicity of interim analyses.
¶ The value is the risk ratio.
‖ Scores on the 15-item quality-of-recovery (QoR-15) scale range from 0 to 150, with higher scores indicating better quality of recovery. The difference is given in points. Data for day 1 were missing for 68 patients in the dexamethasone group and 61 patients in the placebo group. Data for day 30 were missing for 74 patients in the dexamethasone group and 75 patients in the placebo group.
** The value is the median difference.

Subgroup	Dexamethasone	Placebo	Risk Difference (95.6% CI)
	no. of patients/total no. (%)		
All patients	354/4350 (8.1)	394/4328 (9.1)	−0.9 (−2.1 to 0.3)
Diabetes status			
No	289/3767 (7.7)	314/3757 (8.4)	−0.7 (−2.0 to 0.6)
Yes	65/583 (11.1)	80/571 (14.0)	−2.9 (−6.9 to 1.0)
Risk of infection			
Low	174/2577 (6.8)	197/2569 (7.7)	−0.9 (−2.4 to 0.5)
Moderate	148/1509 (9.8)	162/1499 (10.8)	−0.8 (−3.0 to 1.4)
High	32/264 (12.1)	35/259 (13.5)	−1.7 (−7.6 to 4.0)
Sex			
Male	182/2383 (7.6)	207/2366 (8.7)	−1.0 (−2.6 to 0.6)
Female	172/1967 (8.7)	187/1962 (9.5)	−0.8 (−2.6 to 1.1)
Age			
18–47 yr	78/871 (9.0)	90/871 (10.3)	−1.5 (−4.4 to 1.3)
48–57 yr	80/935 (8.6)	82/877 (9.4)	−0.8 (−3.5 to 1.8)
58–65 yr	78/942 (8.3)	84/925 (9.1)	−0.8 (−3.4 to 1.8)
66–71 yr	60/787 (7.6)	68/833 (8.2)	−0.3 (−3.0 to 2.3)
72–96 yr	58/815 (7.1)	70/822 (8.5)	−1.0 (−3.7 to 1.6)
Body-mass index			
<18.5	8/64 (12.5)	3/63 (4.8)	7.0 (−2.5 to 16.2)
18.5 to <25	69/1149 (6.0)	70/1135 (6.2)	0.03 (−2.0 to 2.0)
25 to <30	106/1525 (7.0)	124/1539 (8.1)	−1.1 (−3.1 to 0.7)
30 to <40	135/1341 (10.1)	154/1306 (11.8)	−1.5 (−4.0 to 0.9)
≥40	36/271 (13.3)	43/284 (15.1)	−2.3 (−8.4 to 3.5)
ASA physical status classification			
I–II	228/3112 (7.3)	263/3125 (8.4)	−1.0 (−2.4 to 0.4)
III–IV	126/1238 (10.2)	131/1203 (10.9)	−0.7 (−3.2 to 1.7)
Surgical-wound status			
Clean	221/2935 (7.5)	250/2922 (8.6)	−1.0 (−2.4 to 0.4)
Contaminated	133/1415 (9.4)	144/1406 (10.2)	−0.7 (−3.0 to 1.5)
Current smoker			
No	295/3620 (8.1)	314/3615 (8.7)	−0.4 (−1.7 to 0.9)
Yes	59/730 (8.1)	80/713 (11.2)	−3.5 (−6.6 to −0.4)
Average intraoperative FIO_2			
0.21–0.40	117/1442 (8.1)	118/1414 (8.3)	−0.3 (−2.4 to 1.8)
0.41–0.45	43/522 (8.2)	45/525 (8.6)	−0.1 (−3.5 to 3.2)
0.46–0.50	100/1251 (8.0)	124/1193 (10.4)	−2.0 (−4.4 to 0.3)
0.51–0.56	26/309 (8.4)	35/331 (10.6)	−2.3 (−7.0 to 2.3)
0.57–1.00	68/819 (8.3)	71/855 (8.3)	−0.1 (−2.9 to 2.5)
Duration of surgery			
0.03–1.62 hr	42/901 (4.7)	47/867 (5.4)	−0.6 (−2.7 to 1.5)
1.63–2.17 hr	47/846 (5.6)	72/885 (8.1)	−2.2 (−4.6 to 0.1)
2.18–2.82 hr	72/850 (8.5)	68/866 (7.9)	0.6 (−2.1 to 3.2)
2.83–3.75 hr	79/893 (8.8)	83/866 (9.6)	−0.7 (−3.5 to 2.0)
3.76–12.98 hr	114/860 (13.3)	124/844 (14.7)	−1.5 (−5.0 to 1.8)
Area			
Australia	291/3588 (8.1)	333/3562 (9.3)	−1.2 (−2.5 to 0.1)
Hong Kong	34/476 (7.1)	31/474 (6.5)	0.5 (−2.9 to 3.7)
New Zealand	29/280 (10.4)	30/288 (10.4)	0.6 (−4.5 to 5.6)



in patients with diabetes, −2.9 percentage points [95.6% CI, −6.9 to 1.0]; risk difference in patients without diabetes, −0.7 percentage points [95.6% CI, −2.0 to 0.6]). There was also no compelling evidence of heterogeneity according to the presence or absence of diabetes or according

Figure 2 (facing page). Subgroup Analyses of the Primary Outcome in the Modified Intention-to-Treat Population.
The primary outcome was surgical-site infection within 30 days after surgery. The dashed red line indicates the noninferiority margin of 2.0 percentage points. The widths of the confidence intervals for subgroup analyses were not adjusted for multiplicity and should not be used to infer definitive treatment effects. The body-mass index is the weight in kilograms divided by the square of the height in meters. American Society of Anesthesiologists (ASA) physical status classes range from I to VI, with higher classes indicating more severe systemic disease. South Africa was excluded from the area subgroups because only 10 patients were enrolled at the trial site in that country, and there were no surgical-site infections among these patients. FIO_2 denotes fraction of inspired oxygen.

to other subgroups in the per-protocol or as-treated populations (Figs. S1 and S2).

SECONDARY OUTCOMES

Secondary outcomes are shown in Table 2. The incidences of superficial, deep, or organ-space infections assessed individually were similar in the two groups. The incidence of deep or organ-space surgical-site infections within 90 days after surgery in patients with implanted prosthetic material was also similar in the two groups, when considered separately or together. Sepsis that had occurred by the day of discharge was observed in 0.9% of patients in the dexamethasone group and in 1.5% of patients in the placebo group (risk ratio, 0.58; 95% CI, 0.39 to 0.87). The median QoR-15 scores on day 1 were 109 and 104, respectively (median difference, 5.0 points; 95% CI, 3.8 to 6.2). Chronic postsurgical pain at 6 months after surgery was observed in 8.7% of patients in the dexamethasone group and in 7.1% in the placebo group (risk ratio, 1.23; 95% CI, 1.06 to 1.42).

TERTIARY AND SAFETY OUTCOMES

The results for the tertiary outcomes are presented in Table S9. Nausea and vomiting in the first 24 hours after surgery occurred in 42.2% of patients in the dexamethasone group and in 53.9% in the placebo group (risk ratio, 0.78; 95% CI, 0.75 to 0.82). Safety outcomes and adverse events are reported in Table S13. Hyperglycemic events in patients without diabetes occurred in 22 of 3787 (0.6%) in the dexamethasone group and in 6 of 3776 (0.2%) in the placebo group. The median difference in blood glucose level between the preoperative blood glucose value and the maximum value recorded up to postoperative day 2 was 3.6 mmol per liter (interquartile range, 2.5 to 4.9 [65 mg per deciliter; interquartile range, 45 to 88]) and 2.4 mmol per liter (interquartile range, 1.4 to 3.6 [43 mg per deciliter; interquartile range, 25 to 65]), respectively. Insulin treatment in patients without diabetes was administered to 19 patients (0.5%) in the dexamethasone group and 4 (0.1%) in the placebo group.

DISCUSSION

In this large, pragmatic, noninferiority trial involving patients undergoing nonurgent, noncardiac surgery of 2 hours or more in duration while the patients were under general anesthesia and involving an overnight hospital stay of at least 1 day, a single 8-mg dose of dexamethasone was found to be noninferior to placebo with respect to the primary outcome of surgical-site infection within 30 days after surgery. This finding was consistent across all prespecified subgroups, including patients with or without diabetes mellitus, and held true for the individual subtypes of surgical-site infections.

Long-term glucocorticoid therapy is associated with an increased risk of surgical-site infection and wound dehiscence.[18-19] There has therefore been concern that a single intraoperative dose of dexamethasone could influence the risk of surgical-site infections because it has a biologic half-life of up to 72 hours[20] and leads to innate immune-cell gene expression and activation effects.[5] Previous trials have not shown an increase in the risk of infection associated with the use of dexamethasone.[21-23] These trials either used multiple doses of dexamethasone and examined composite end points[23] or administered a single intraoperative dose that was smaller than that used in our trial.[21] Some trials also excluded patients with diabetes mellitus[22] or did not examine the risk of surgical-site infection as the primary outcome.[21-23] We assessed a single 8-mg dose of dexamethasone because this dose is commonly used in practice and has additional analgesic benefits over the 4-mg dose when used as an antiemetic.[1,3]

The percentage of patients with surgical-site infection at 30 days in this trial involving patients undergoing noncardiac surgery was 8.1% in the dexamethasone group and 9.1% in the placebo group. These results are consistent with the findings in a placebo-controlled, randomized trial that assessed the effects of a larger dose of dexamethasone in patients undergoing cardiac surgery. In that trial, the incidence of wound infection appeared to be similar in the two groups; however, the overall risk of all postoperative infections was lower in the dexamethasone group than in the placebo group.[24] Our observation that the results in the subgroup of patients with diabetes mellitus were similar to those of the primary analysis is reassuring, since patients with diabetes are at a higher risk for complications related to infection and for hyperglycemia, and there is therefore reluctance to use dexamethasone in patients with diabetes.[3,7] The percentage of patients with diabetes in this trial (13.2%) was at the lower end of previous reports in patients who had undergone noncardiac surgery (14 to 19%).[25,26] This may be because of the lower prevalence of diabetes in our population than in the predominantly North American populations in previous trials.[27]

Limitations of our trial warrant attention. Nonadherence to the assigned treatment may bias the analyses in the modified intention-to-treat population toward noninferiority. However, nonadherence was low and was similar in the two groups (6.3% in the dexamethasone group and 6.6% in the placebo group). Nonadherence was largely explained by the administration of supplemental nontrial glucocorticoids in the postoperative period, which underscores the common use of postoperative glucocorticoids in practice for wound-related issues such as ongoing pain or swelling. The analyses in the per-protocol and as-treated populations similarly supported the noninferiority of dexamethasone, although these results do not represent comparisons of trial groups according to randomized assignment. In addition, in this pragmatic trial, we did not collect data on perioperative factors that might influence the risk of surgical-site infection, such as subtypes of gastrointestinal surgery, the types of preoperative bowel and skin preparation, or wound treatment and details of perioperative antibiotic prophylaxis (drug class and duration of treatment). In a trial of this size, however, we would expect these factors to be evenly distributed between the groups. It is possible that the postoperative surveillance may have missed some mild infections among patients who did not return for further treatment, but we would expect such events to have been uncommon and unlikely to have altered our findings.

We found no evidence of differences between the groups in the prespecified safety outcomes. Higher differences in the blood glucose level between the preoperative blood glucose value and the maximum value in the dexamethasone group and a higher incidence of hyperglycemic events and insulin use in patients without diabetes are expected consequences of treatment with dexamethasone. The apparent increase in the incidence of new-onset chronic postsurgical pain is an unexpected finding that has not been identified in previous studies.[28] We did not adjust for multiplicity, and this finding may be explained by chance. Future analyses will further assess pain and disability outcomes. Tertiary analyses supported reductions in the risk of nausea and the use of antiemetics in the first 24 hours after surgery associated with dexamethasone, a finding consistent with previous reports.[1-3,22]

In patients undergoing nonurgent, noncardiac surgery involving general anesthesia, a single 8-mg intraoperative dose of dexamethasone was noninferior to placebo with respect to the risk of surgical-site infection within 30 days after surgery.

Supported by a grant (APP1079501) from the Australian National Health and Medical Research Council (NHMRC), a grant (GRF 14101816) from the Research Grants Council of Hong Kong, and Monash University. Dr. Corcoran was supported by a Health Department of Western Australia Raine Foundation Clinical Practitioner Fellowship, Dr. Myles by an NHMRC Practitioner Fellowship (GNT1135937), and Dr. Cheng by an NHMRC Career Development Fellowship.

Disclosure forms provided by the authors are available at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Jaspreet Sidhu for managing the trial; Adam Meehan for data management, construction of the Web-based electronic database, and provision of the Web-based randomization service; Karen Goulding for assistance and advice regarding graphic representation and the provision of support services for the data and safety monitoring committee; Chris Frampton, Mark Williams, and all members of the committees overseeing the trial; and the Australian and New Zealand College of Anaesthetists Clinical Trials Network.

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