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The perioperative administration of dexamethasone and infection (PADDI) trial protocol: rationale and design of a pragmatic multicentre non-inferiority study

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ABSTRACT

Introduction The intraoperative administration of dexamethasone for prophylaxis against postoperative nausea and vomiting is a common and recommended practice. The safety of the administration of this immunosuppressive agent at a time of significant immunological disruption has not been rigorously evaluated in terms of infective complications.

Methods/analysis This is a pragmatic, multicentre, randomised, controlled, non-inferiority trial. A total of 8880 patients undergoing elective major surgery will be enrolled. Participants will be randomly allocated to receive either dexamethasone 8 mg or placebo intravenously following the induction of anaesthesia in a 1:1 ratio, stratified by centre and diabetes status. Patient enrolment into the trial is ongoing. The primary outcome is surgical site infection at 30 days following surgery, defined according to the Centre for Disease Control criteria.

Ethics/dissemination The PADDI trial has been approved by the ethics committees of over 45 participating sites in Australia, New Zealand, Hong Kong, South Africa and the Netherlands. The trial has been endorsed by the Australia and New Zealand College of Anaesthetists Clinical Trials Network and the Australian Society for Infectious Diseases Clinical Research Network. Participant recruitment began in March 2016 and is expected to be complete in mid-2019. Publication of the results of the PADDI trial is anticipated to occur in early 2020.

Trial registration number ACTRN12614001226695.

BACKGROUND
Healthcare-associated infections and diabetes mellitus

At least 200 000 healthcare-associated infections (HAI) are diagnosed in Australian hospital patients each year, occupying 2 million bed-days and costing A\$1 billion per annum.[1] They represent a major global cause

Strengths and limitations of this study

► This is the first large randomised trial evaluating the safety of dexamethasone administration in the intraoperative period in terms of surgical site infection at 30 days following surgery, which will be rigorously evaluated according to clear criteria.

► The pragmatic, multicentre, stratified non-inferiority design and broad inclusion criteria will support external validity across a range of surgical procedures and patient comorbidities, but will not provide evidence regarding paediatric, obstetric or cardiac surgical patients.

► Stratification according to diabetes status will permit evaluation of safety in this vulnerable patient group.

► The trial has 90% power to detect non-inferiority of dexamethasone with a margin of 2% absolute difference in SSI rates.

of morbidity, mortality and excess health expenditure.[2] Surgical site infection (SSI) accounts for the majority of such infections in surgical patients, and can affect long-term mortality.[2–4] SSI can complicate up to 10% of surgical episodes, but rates are under-reported because of variable postdischarge surveillance.[5] Patient factors, laboratory values and operative characteristics can all be used to predict the occurrence of an SSI.[6] In one large retrospective audit, diabetes and chronic glucocorticoid consumption were both suggested to be associated with an increased risk of postoperative infection,[6] and diabetes is an independent risk factor used to predict the risk of SSI.[6] Patients with diabetes are more likely to undergo surgical

procedures and are over-represented in the hospital population.[7–9] They experience more adverse outcomes perioperatively than their non-diabetic counterparts with an increase in associated costs.[7 8] Overall, surgical patients with diabetes have a 35% greater risk of adverse events than those without diabetes[10] and a 6.4% absolute increase in the risk of death compared with matched patients without diabetes.[11] Perioperative hyperglycaemia confounds the relationship between diabetes and perioperative risk.

Dexamethasone administration in surgical patients

Dexamethasone is a synthetic glucocorticoid with potent anti-inflammatory and metabolic effects. It is frequently administered in the perioperative period, most commonly for prophylaxis and treatment of postoperative nausea and vomiting (PONV).[12] PONV is a major problem in perioperative care occurring in 25%–30% of all surgical patients, and up to 70%–80% in high-risk populations (eg, tonsillectomy, strabismus and laparoscopic surgery) without prophylaxis,[13 14] and it adversely affects patient satisfaction with care.[15] The antiemetic mechanisms of dexamethasone are unknown but may include anti-inflammatory actions in the gastrointestinal tract, inhibition of brainstem enkephalin release and modification of central prostaglandin and serotonin synthesis.[16] The number-needed-to-treat for prophylaxis is approximately four.[16] International guidelines recommend a prophylactic intravenous (IV) dose of 4 to 5 mg for adults, but 8 mg is recommended as having additional analgesic benefits.[14] In a survey of a selection of fellows of the Australian and New Zealand College of Anaesthetists (ANZCA) we found that at least 60% of all respondents routinely administer dexamethasone, principally as an antiemetic, to most non-cardiac surgical patients. This practice is supported by a large randomised controlled efficacy trial,[17] meta-analyses[12 18] and international clinical practice guidelines.[14]

Dexamethasone and hyperglycaemia in surgical patients

Blood glucose values exceeding 10 mmol/L are common (up to 40%) after surgery—a phenomenon labelled stress-induced hyperglycaemia (SIH).[19] It is reported to be associated with an increased risk of mortality and complications, including poor wound healing and anastomotic failure for both patients with and without diabetes.[10 20 21] In a surgical cohort hyperglycaemia increased perioperative risk only in patients without diabetes.[22] Overall, the available data suggest that perioperative hyperglycaemia, particularly in patients without diabetes, may not be innocuous and may carry an increase in morbidity and mortality.[23] Glucocorticoids can cause hyperglycaemia[24] but studies in non-cardiac surgical patients have demonstrated inconsistent effects on blood glucose[25 26] and plasma cortisol concentrations.[25] Two recent trials have produced contrasting results.[27 28] In our recent randomised trial (The Perioperative Administration of Dexamethasone and Glucose (PADDAG)

trial, T Corcoran), we identified a hyperglycaemic effect of 8 mg of dexamethasone only in patients with diabetes, which is consistent with Tien's findings that dexamethasone 8 mg was associated with a 3.3 mmol/L increase in blood glucose concentrations within 24 hours of surgery in patients with diabetes.[29] Other volunteer and clinical studies have demonstrated no effect on blood glucose concentrations.[30 31] There is therefore considerable uncertainty as to the dysglycaemic effect of a single dose of dexamethasone.

The safety of perioperative dexamethasone administration

Although glucocorticoid use in cardiac surgery has been shown to be both beneficial and safe,[32] comparable large randomised controlled trials in non-cardiac surgical patients are lacking. A retrospective case–control study suggested that dexamethasone increases infection risk[33] while a retrospective cohort study did not confirm these findings.[34] Two small randomised trials also failed to demonstrate an association between dexamethasone use and infection.[35 36] One was prematurely terminated and both were underpowered.[37] A recent large trial of the antiemetic effectiveness of dexamethasone 8 mg in 1350 patients undergoing colorectal surgery confirmed the antiemetic effect of dexamethasone but infective outcomes were not specifically interrogated.[38] Significant concern has been expressed regarding the safety of the administration of dexamethasone in the perioperative period in patients undergoing non-cardiac surgery.[39–41] Although meta-analyses have asserted the safety of perioperative glucocorticoids, even in very large doses,[12 16 42 43] the clinical trials to date are antiemetic efficacy studies. Few have examined the long-term side effects or eventual patient outcomes and none of these studies were adequately powered for infection. The subsequent meta-analyses therefore give an unwarranted impression of the safety profile of perioperative dexamethasone. We reached a comparable conclusion to others, which is that there was no signal of harm, but that current trials were too small, underpowered and did not include important safety endpoints (such as wound infection) as a primary endpoint.[44 45] We have therefore designed a trial to address this question.

Why a non-inferiority trial?

Noninferiority trials are increasingly used to evaluate whether effective treatments are safe.[46 47] We chose to employ this study design, despite an increase in the complexity associated with statistical analysis and a larger sample size than would be required for a conventional superiority or equivalence trial. The justification for the design is that antiemetic effectiveness, which is the principal indication of the use of intraoperative dexamethasone, has already been demonstrated. We chose an absolute non-inferiority margin (△) of 2% which was agreed by the steering committee using the Delphi method, as the literature is clearly inconsistent. An absolute increase in risk of infection of 2% produces a number

needed to harm (NNH) of 50. This was considered the maximum acceptable absolute increase in infection risk that could be tolerated to conclude non-inferiority.

METHODS

We used the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials checklist when writing our report).[48] This protocol has been submitted to the ethics committee (or relevant regulatory body) at each site and their approval obtained. The trial sponsor is Alfred Health, Melbourne, and the trial was approved by the Alfred Hospital Ethics Committee in September 2015 (HREC/15/Alfred/22 (Local reference: 334/15)). The trial is registered in the Australia and New Zealand Clinical Trials Registry (ANZCTR); registration number ACTRN12614001226695. The trial start date is 10 March 2016, and the anticipated end date is 30 July 2019.

Study design

PADDI is a large (n=8880), multicentre, pragmatic, parallel assessment, triple-blinded (Patient, Anaesthetist and Assessor) placebo-controlled non-inferiority trial, with patients randomised to receive either dexamethasone 8 mg (Dex group) or matched placebo (Control group) intravenously after the induction of anaesthesia. Group allocation is stratified by diabetes status and site.

Study hypothesis

The intraoperative use of dexamethasone 8 mg in adult patients undergoing elective non-cardiac surgery is non-inferior compared with placebo in relation to the incidence of surgical site infection up to 30 days after surgery.

Participants and enrolment

We plan to recruit patients undergoing elective, non-cardiac surgery under general anaesthesia with a planned surgical duration of greater than 2 hours and more than one overnight stay in hospital.

Inclusion and exclusion criteria are listed in box 1.

Full informed consent will be provided by participants prior to enrolment. Randomisation will be conducted by a random number generator, in permuted blocks of size six, stratified by centre, and allocation concealment will be maintained by a web-page randomisation and allocation portal (https://www.paddi.org.au/). Following enrolment, on the day of surgery, patients are randomly assigned (1:1) to groups via a web-based service, stratified by site and diabetic status. All other perioperative clinical care is according to standard practice. All relevant factors are recorded on the trial case report form.

Perioperative management

Diagrammatic representation of participant flow through the trial processes are illustrated in figure 1. Patients are asked to complete the 12-item version of the WHO Disability Assessment Schedule (WHODAS) preoperatively. All patients receive prophylactic antibiotics

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Box 1 Inclusion and exclusion criteria

Inclusion criteria
- ► Adult patients ≥18 years of age
- ► American Society of Anesthesiologists (ASA) physical status 2–4
- ► Elective or expedited non-cardiac surgery of at least 2 hours duration under general anaesthesia (±regional block)
- ► Requiring a hospital stay of at least one postoperative night
- ► A surgical skin incision >5 cm in length or multiple incisions with a total incision length of >5 cm.

Exclusion criteria
- ► Poorly controlled diabetes (HbA1c>9.0%)
- ► Endovascular procedure with a small (<5 cm length) skin incision
- ► Ophthalmic surgery
- ► Planned dexamethasone (or other corticosteroid) therapy (eg, history of intractable PONV, maxillofacial surgery, intracranial neurosurgery)
- ► Recent (<2 weeks since end of treatment) infective episode requiring treatment with antibiotics
- ► Chronic antibiotic therapy (eg, for bronchiectasis, cystic fibrosis etc)
- ► When surgery is indicated for an infective process (eg, infected joint prosthesis)
- ► A history of allergy or adverse reaction to glucocorticoids
- ► Planned postoperative intubation or ventilation
- ► Concurrent immunosuppressive therapies
- ► Current or recent (within preceding 1 month) systemic use of glucocorticoids
- ► Surgical procedures within the preceding 2 months
- ► Known immunosuppressed state
- ► Known moderate or severe liver disease (Hepatitis A, B, C, with cirrhotic liver states, primary biliary cirrhosis, sclerosing cholangitis—any of these with portal hypertension and/or variceal bleeding)
- ► Dialysis-dependent renal failure
- ► When the index surgical procedure is expected to require a further surgical procedure within the subsequent 30 days.
- ► Metastatic cancer
- ► Pregnant and lactating women

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according to established guidelines. Patients in the diabetes stratum have a glycated haemoglobin (HbA1c) value measured prior to surgery. Perioperative care for diabetes patients, including management of perioperative diabetes medications and perioperative blood glucose measurements are delivered according to local protocols. Upon the insertion of a cannula, all patients have a point-of-care (POC) blood glucose value measured. A POC blood glucose measurement is also performed on arrival to the post-anaesthesia care unit (PACU) and at 8 to 12 hours following study drug administration (irrespective of whether this is an intraoperative or postoperative sample). These values will be fasting samples. On day one postoperatively, all patients have a POC blood glucose value determined. The protocol does not stipulate that the day one POC blood glucose values have to be measures in the fasted state. The protocol also does not stipulate whether the POC values will be measured on arterial, venous or capillary blood, nor does it stipulate which devices are to be used. In this very large trial, we expect that the law of numbers will produce balance of these measures among the groups. Hence, these values

will all be recorded and included in the tertiary analysis. On day two postoperatively, all patients still hospitalised have a C-reactive protein (CRP) concentration measured. Additional laboratory tests are ordered as dictated by clinical need and local practice.

The study drug phial (2 mL) is supplied to the attending anaesthetist, and is administered as an intravenous bolus within 5 min after the induction of anaesthesia. Choice of anaesthetic agents, antiemetics and perioperative analgesia are left to the discretion of the anaesthetist and is recorded. Patients are followed daily and outcomes are recorded until discharge. On day one all patients are asked to complete the 15-item quality of recovery score (QoR-15).[49] In the PACU and on days one to three, pain and nausea severity are assessed using numerical rating scales. The number of vomiting episodes and use of antiemetic agents is also recorded. A wound assessment questionnaire is completed on day three and on the day of discharge. Safety data are collected throughout the entire study period and at 30 days. Thirty days after surgery, all patients are contacted by phone to ascertain whether they have experienced any outcomes, and if detected, further testing is arranged. Documentation for such events is sought in the hospital medical record and doctor's records. The QoR-15 is repeated on day 30 along with WHODAS V.2.0, and the WHODAS V.2.0 is repeated 6 months after surgery to ascertain survival status and new-onset disability. At 6 months, patients are asked whether there is pain in the surgical site. If the answer is affirmative, they are asked to complete a modified Brief Pain Inventory-Short Form (mBPI-SF) and Neuropathic Pain Questionnaires. Additional dexamethasone (or other glucocorticoid) is prohibited for the 30-day study period following surgery.

Data collection: data entry and auditing

Patients are blinded to group allocation. Anaesthetists, surgeons and research staff collecting data have no knowledge of group identity. Study data are collected in a paper-based case report form, for transcription onto a web database. Random audits of centres are performed throughout the conduct of the trial, aiming to assess the accuracy and legitimacy of the trial data, and to confirm compliance with Good Clinical Practice. All study personnel have 24 hours access to the study coordinating centre to resolve any questions that arise. All data will be stored on an independent server and regularly backed up to at least one other source. The steering committee will have access to all trial data sets and all requests for post-trial data release will require consideration and authorisation by the committee.

Trial management

The PADDI Trial Project Office is located in the ANZCA Clinical Trials Network office in the Department of Epidemiology and Preventive Medicine at Monash University, Melbourne, Victoria, Australia. The PADDI Trial Steering Committee is the governance body for the trial and oversees all aspects of its operation.

Data monitoring

We established an independent data safety and monitoring committee (DSMC), consisting of an experienced academic clinical trials statistician (as chair), intensive care physician, anaesthetist, endocrinologist and an independent statistician/clinical epidemiologist. The responsibilities of the DSMC include review and provision of advice on the trial protocol, review and interpretation of accruing data, the performance of interim analyses, and ensuring the safety of the trial participants and the integrity of the trial data.

Unblinding process

A 24-hour telephone number is provided to sites to facilitate emergency unblinding of individual treatment. Provisions are made whereby any unblinding request is initially validated in terms of clinical imperative. Subsequent to this verification, the database manager provides the treatment code to the contact individual at the requesting site. The trial coordinators, and investigators remain blinded to treatment received.

Endpoint adjudication Committee

An Independent Endpoint Adjudication Committee (IEAC) comprising experienced perioperative physicians has been established to resolve any uncertainty relating to the primary trial endpoint. This comprises a chair (experienced anaesthetist), two infectious disease clinicians and an endocrinologist. A custom algorithm is built into the database and endpoint submission form, to ensure that reports of endpoints either comply with Centres for Disease Control (CDC) criteria, or, where deficient, to prompt a request for further information. Where compliance with endpoint criteria is equivocal, the chairman of the IEAC consults with other specialist members of the committee. Such adjudication processes are completely independent of any input from the trial management team.

Trial endpoint definitions
The primary endpoint

The primary endpoint for the trial is the occurrence of a surgical site infection within 30 days of the day of surgery. The SSI definitions employed are those defined by the CDC criteria,[50] incorporating modifications instituted in January 2016. These definitions employ five separate categories of SSI, (Superficial Incisional Primary, Superficial Incisional Secondary, Deep Incisional Primary, Deep Incisional Secondary and Organ Space infection).

The secondary and tertiary endpoint definitions are as per box 2.

A separate analysis will be performed to examine the data regarding the nature and characteristics of chronic post-surgical pain (CPSP). These data will be submitted as a manuscript for publication distinct from the main manuscript.

Box 2 Secondary and tertiary endpoints

Secondary endpoints

1. Superficial, deep and organ space infections within 30 days, considered separately
2. Surgical site infection (as per the primary endpoint definition) including deep and organ space infections occurring within 90 days in patients receiving prosthetic material during surgery.
3. Other infections (composite including urinary tract infections, pneumonia and catheter related infections) and sepsis (All of these will comply with CDC criteria for definition of infections at each site).
4. Quality of recovery: QoR-15 score on days 1 and 30
5. Chronic Post-Surgical Pain (CPSP) (at 6 months) - will be defined as pain reported by the patient at the 6 months follow-up, in the area of the index surgery which was not present prior to surgery
6. Death or new onset disability within 6 months following surgery. Defined as a 4-point (8%) or greater increase in the 12-item WHODAS 2.0 score at both 30 days and 6 months compared with baseline (preoperative) score.

Tertiary endpoints

1. Nausea (0–24 hours) - Worst nausea as measured on a numerical rating scale (numerical rating scale [NRS], 0–10) in PACU; in the first 24 hours following surgery and post-PACU, on day 2, and on day 3. Antiemetic usage in each of these periods.
2. Vomiting (0–24 hours) - Vomiting (occurrence and number of events) in PACU and within first 24 hours following surgery post-PACU, on day 2 and on day 3. Antiemetic usage in each of these periods.
3. Highest pain score (NRS, 0–10) at rest and on movement in PACU and in the first 24 hours post-PACU
4. Hospital stay: from the start (date, time) of surgery until discharge from acute care facility.
5. CRP concentration - day 2 postop.
6. Glycemic control (defined as the maximal changes in perioperative blood glucose from baseline up to day 2 postoperatively, and the influence of HbA1c value on this change in both strata)
7. Hypoglycaemic event rates - a hypoglycaemic event being defined as a blood glucose recording less than 4.0 mmol/L.
8. Hyperglycaemic event rates in patients without diabetes - a hyperglycaemic event being defined as a blood glucose recording greater than 10 mmol/L.
9. Insulin use rates in patients without diabetes
10. Lymphocyte and neutrophil levels - Change in neutrophil-to-lymphocyte ratios from baseline to days 1 and 2
11. Rates of safety outcomes (unexpected reoperation, unplanned readmission to hospital, myocardial infarction, cerebrovascular accident, deep venous thrombosis, pulmonary embolism, mortality at 30 days and mortality at 6 months), serious adverse events, and severity of adverse events (mild, moderate, severe), classified by organ system

Substudies

Four separate substudies are planned for the trial. They are:

a. Baroreceptor reflex substudy
b. Genomic substudy
c. Severe PONV substudy
d. Sleep substudy

Because the original model consent form did not specifically address genetic studies, participants will be asked to sign an additional consent form to document their consent to the collection and submission of additional blood samples for storage and future testing (including genetic analysis).

Sample size

Sample size calculations for this non-inferiority trial are based on a null hypothesis of H_O: p2–p1 >delta (ie, inferior); where p1 is the proportion of patients expected to experience the SSI outcome in the placebo arm, p2 is the proportion in the dexamethasone arm, and the non-inferiority margin delta is 2%. The ENIGMA-II trial (n=7000) had an SSI rate of 9.2%, without post-discharge surveillance.[5] Infection rates up to 25.4% have been observed in higher risk cohorts.[51] With an infection rate of 9% in each arm, 4303 patients per intervention arm are required to detect the non-inferiority margin of 2% with 90% probability (power), where non-inferiority is concluded if the upper endpoint of the two-sided 95% CI for the difference in infection rates is less than 2%. Harm will be declared if the lower endpoint of the two-sided CI lies completely above +2%. Target recruitment will be set at 8880 to account for 2% losses to follow-up.

To assess the impact on sample size of the proposed two interim analyses (after 1/3 and 2/3 of patients are recruited, see below), a numerical simulation assessment with 20 000 replications indicated that, with 4303 completed patients per intervention arm (up to a simulation SE of +/-0.1%):

▶ When the true event rates are 9% in each arm, the probability of correctly declaring non-inferiority (power) is 90.0%, and the probability of (falsely) declaring harm is <0.1%.
▶ When the true event rates are 9% in the placebo arm and 11% in the Dex arm, representing the threshold for harm, the probability of falsely declaring non-inferiority is 2.5%, and the probability of (falsely) declaring harm is 2.6%.
▶ When the true event rates are 9% in the placebo arm and 13% in the Dex arm, representing clear harm, the probability of falsely declaring non-inferiority is <0.1%, and the probability of (correctly) declaring harm is 83%.

STATISTICAL ANALYSIS

The analysis and reporting of the results will follow the CONSORT guidelines.[52] Baseline characteristics will be tabulated by using appropriate summary statistics. Data will be analysed according to the intention-to-treat (ITT) principle and secondarily with the per protocol (PP) population and as-treated (AT) populations (see definitions and details below).

A. Modified ITT principle

We will employ a modified ITT (mITT) principle for the purpose of the primary trial analysis. The mITT population will consist of all randomised patients who undergo induction of anaesthesia and eligible surgery (surgery

	Pre Op	Intra Op	PACU	Post Op	Day 1	Day 2	Day 3	Day of Discharge	Day 30	Six months
Screening, Informed Consent, Randomisation	X									
Demographics	X									
WHODAS	X								X	X
Pre-op bloods: HbA1c	X									
Post-op bloods: CRP							X			
Intra-operative information		X								
Pain and PONV - NRS, Highest temperature, Antiemetic usage			X	X	X	X Only if in-patient	X Only if in-patient			
Point of Care Glucose (Patients with DM)	X (on cannula insertion)	X (hourly / as per protocol)	X On arrival to PACU	As per Therapeutic Flowcharts 2 and 3 OR local perioperative diabetes management protocols (note: this will include the 8-12 hours post study drug BGL)	X As per NPS standards	X As per NPS standards	X As per NPS standards			
Point of Care Glucose (Patients without DM)	X (at time of HbA1c collection)		X On arrival to PACU	8 to 12 hours BGL post study drug administration	X					
Wound information							X Only if in-patient	X	X	
QoR15					X				X	
mBPI, Neuropathic Pain Questionnaire										X (if applicable)
Safety Data Collection		X		X	X			X	X	

*Note: for patients with Diabetes – the HbA1c and BGLs should be taken as standard of care.
Other pre-op and post-op bloods taken as standard of care will be documented in the CRF. These include FBC, Creatinine, CRP.

Figure 1 Diagrammatic representation of trial processes.

with a total surgical incision length >5 cms). This is an arbitrary incision length, chosen by means of a Delphi approach among the members of the trial steering committee. These patients will be analysed according to the group to which they were randomised, whether they receive study drug or not, or whether they receive additional (non-study) glucocorticoid or not. The only exclusions will be for:

a. patients who do not undergo surgery
b. patients who undergo surgery where the incision length <5 cm
c. patients who are found to have an existing infection at any site at the time of surgery.

Patients who have consent withdrawn will have their data used up until the time of withdrawal.

Primary endpoint analysis
30-Day SSI rate
The absolute difference in 30 day infection rates will be summarised with a two-sided, asymmetric CI, adjusted for multiplicity of interim analysis assessments to preserve an overall 95% CI. This will be performed using binomial-identity regression, adjusting for diabetic status. Non-inferiority will be declared if the difference in infection rates (dexamethasone – placebo) lies entirely below the non-inferiority margin of +2%. Sensitivity of results to missing outcome data will use multiple imputation with chained equations.

Secondary and tertiary endpoint analyses
Secondary endpoints will be compared across dexamethasone and placebo arms using regression models adjusted for diabetic status. Binary outcomes will use log-binomial regression to estimate risk ratios together with 95% CIs, or exact logistic regression to approximate these values if the number of events in either arm is fewer than 10. Count outcomes will use Poisson regression with robust standard errors to account for over-dispersion. Continuous outcomes will use linear regression with robust standard errors. Skewed continuous outcomes will be summarised as median and interquartile ranges and difference between medians with 95% CIs computed via quantile regression. Hospital length of stay will be tested across arms using the Wilcoxon–Breslow–Gehan test and HR estimated using Cox proportional hazards regression, with data censored at 30 days and in-hospital deaths assigned the longest duration of stay

Subgroup analyses
Planned subgroup analyses will assess consistency of differences between dexamethasone and placebo arms with respect to primary and secondary outcomes. These will be assessed using regression models with subgroup-by-randomised arm interaction terms:
► Diabetic status
► Risk of infection; this comprises a summary of points awarded to risk status classified as low, moderate and

high risk (0–1, 2–3>3 points); where one point is awarded for each of:

- – Age >70 years
- – ASA physical status >3
- – Diabetes status=Yes
- – BMI >35 kg/m^2
- – Wound status other than "clean"
- – Surgery involving the gastrointestinal tract
- ► Sex
- ► Age (approximate quintiles)
- ► Country

Additional prespecified subgroups will be tested for heterogeneity of effect, and their results considered exploratory (only): body mass index categories (underweight, normal, overweight, obese, super obese), ASA physical status (1/2, 3, 4), wound classification, smoking status, average intraoperative oxygen concentration during anaesthesia (approximate quintiles), duration of surgery (approximate quintiles) and colorectal or gastrointestinal surgery.

Adverse events
Adverse events for non-outcome variables will be tabulated by treatment arm, organ system and severity.

Adjustments for multiplicity of endpoints
The primary outcome will be adjusted for multiple interim analyses as detailed below in the Interim Analysis section below. Results for secondary endpoints will be reported with 95% CIs and unadjusted p values, together with their corresponding threshold significance levels using the Bonferroni-Holm procedure for controlling for multiplicity.[53] These were calculated to produce a familywise type I error rate of 5% across all secondary endpoints. Tertiary outcomes will be reported with 95% CIs, without any corresponding p values.

Additional sensitivity analyses
Sensitivity analyses for all outcomes will use regression models with additional adjustment for the stratification variable of site using random or fixed effects models, plus post-hoc adjustment for any variables exhibiting substantial imbalance across treatment arms at baseline.

PP and AT population definitions and analyses
B. PP principle
PP population definition
PP population will comprise those patients who completed the treatment to which they were originally allocated, meaning ONLY those patients who receive a single dose of study drug or placebo according to their original randomised allocation. This analysis specifically *excludes* patients who were not given their randomised study drug at commencement of surgery AND patients who receive their study drug but also receive non-study glucocorticoid within the 30 days following surgery. This also excludes patients randomised to dexamethasone whose randomisation was overridden and received open-label dexamethasone within the 30 days following surgery. Patients who

withdraw consent will have their data used up until the time of withdrawal.

PP analysis
The PP analysis will use the same methods as the mITT analysis, confined to the patients meeting PP population definition. Patients whose diabetic status was incorrectly classified at the time of randomisation will still be analysed according to their classification at randomisation.

C. AT principle
AT population definition
The AT population will consist of all patients in the mITT population but with treatment arm determined according to their treatment actually received. Specifically:
a. Patients will be regarded as treated with dexamethasone if:
1. they receive dexamethasone as randomised
2. their randomisation is ignored (over-ridden) and they receive an initial dose of open-label dexamethasone (or other glucocorticoid)
3. they receive postrandomisation open-label dexamethasone (or other glucocorticoid), regardless of their randomised allocation

[Note that patients receiving randomised dexamethasone plus later open label dexamethasone (or other glucocorticoid) are included in (3) above.]
b. Patients will be regarded as not treated with dexamethasone if:
1. They are randomised to placebo and receive placebo, and do not receive open label dexamethasone (or other glucocorticoid) at any time
2. They are randomised to dexamethasone but do not receive it initially, and do not receive any later open label dexamethasone (or other glucocorticoid)

Patients who withdraw consent will have their data used up until the time of withdrawal.

AT analysis
The AT analysis will use the same methods as the mITT analysis, with treatment arm defined as treatment received according to the AT population definition. The true diabetic status of each patient, as opposed to the classification at the time of randomisation, will be used in the analysis.

Sensitivity analyses
PP analysis
Because the patients not meeting the PP population definition have been excluded, there may no longer be balance in patient characteristics between dexamethasone and placebo arms. The baseline and pre-operative characteristics in the dexamethasone and placebo arms will be tabulated and compared for the 'compliant' (PP) patients. Any variables exhibiting imbalance will be adjusted for as covariates in the risk-difference regression. Should this model fail to converge, a linear model with identity link and robust standard errors will be fit.

AT analysis

Patients receiving dexamethasone and patients receiving placebo (or no treatment) according to the above definitions may not be balanced for patient characteristics. The baseline and pre-operative characteristics in patients receiving dexamethasone and receiving placebo will be tabulated and compared. Any variables exhibiting imbalance will be adjusted for as covariates in the risk-difference regression. Should this model fail to converge, a linear model with identity link and robust standard errors will be fitted.

Details of interim analyses and boundaries

Interim analyses for assessment of non-inferiority and harm of the primary outcome will be performed after enrolment of 2960 and 5920 patients (1/3 and 2/3 of total recruitment) using two-sided repeated asymmetric CIs. The primary analysis will use the mITT population defined above. Asymmetrical stopping boundaries will be used, as the clinical significance of a signal indicating harm is felt to be more important than the lack of harm. Non-inferiority will be declared at a particular time point if the upper endpoint of the CI for the difference in infection rates (dexamethasone minus placebo) is less than 2%. Harm will be declared if the lower endpoint of the CI lies above 2%. The upper endpoint of the CI for consideration of non-inferiority will be based on the O'Brien-Fleming spending function. The lower endpoint of the CI for consideration of harm will be based on the less conservative Power function with parameter 2. CI at any time point is then defined as (estimate $-Z_{LOWER}$ SE, estimate $+Z_{UPPER}$ SE). At (information) fractions of 33%, 67% and 100% of patients, the upper Z values for non-inferiority are 3.71, 2.51 and 1.99, respectively, and the lower Z values for harm are 2.77, 2.35 and 2.06.

The analysis of the primary endpoint will be repeated for the PP population and the AT population, using the same boundaries as for the mITT population. The boundaries will be adjusted according to the actual number of patients randomised at the time of each interim analysis. Should the result cross a designated boundary at an interim analysis, consideration will be given by the DSMC to terminate the trial <u>if</u> the committee believes the interim results are sufficiently compelling to change practice around the world

Availability of the statistical analysis plan

A detailed Statistical Analysis Plan will be made available on the trial's website (https://www.paddi.org.au). It will be finalised prior to database lock and unblinding of treatment arms.

Protocol amendments

In November 2018, the trial steering committee elected to change the inclusion criteria to exclude any further recruitment of patients with ASA status=1 (thus limiting further recruitment to patients with ASA status 2–4). The purpose was to include a larger number of patients with greater comorbidities. The proposed amendment was approved by the DSMC. The current protocol version is Number 2.4 (dated 7 November 2018).

ETHICS AND DISSEMINATION

The rationale and design of the PADDI trial has been presented at more than five international anaesthesia, intensive care medicine and surgical meetings over the past 5 years. The trial has been approved by the ethics committees of over 45 participating sites in Australia, New Zealand, Hong Kong, South Africa and the Netherlands. Final results are expected to be presented at one or more international scientific meetings in 2020 and 2021. The main results of the trial are expected to be published in a major medical journal in 2020. There are no plans to provide public access to the participant-level database. The trial has been endorsed by the Australia and New Zealand College of Anaesthetists Clinical Trials Network, and the Australian Society for Infectious Diseases Clinical Research Network, and it has received a project grant from the National Medical Health and Research Council of Australia.

Patient and public involvement statement

Patients were not involved in the design of this research. When the trial has completed recruitment, has been analysed fully and the manuscript published, participants will be informed of the results through the dedicated trial website (www.paddi.org.au).The results of the study will be presented in a study newsletter suitable for a non-specialist audience.

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