The Perioperative ADministration of Dexamethasone and Infection (PADDI) trial

Statistical analysis plan

Version 1.1

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An international collaborative project endorsed by the Australian and New Zealand College of Anaesthetists Clinical Trials Network (ANZCA-CTN) and the Australian Society of Infectious Diseases (ASID).

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ABBREVIATIONS

AE	Adverse event
ANZCA	Australian and New Zealand College of Anaesthetists
ANZCA CTN	Australian and New Zealand College of Anaesthetists Clinical Trials Network
ASA	American Society of Anesthesiologists
CDC	Centers for Disease Control and Prevention
CONSORT	CONsolidated Standards of Reporting Trials
CPSP	Chronic postsurgical pain
CRP	C-reactive protein
DM	Diabetes mellitus
DS	Diabetic stratum
DSMC	Data Safety and Monitoring Committee
DVT	Deep vein thrombosis
ENIGMA-II	The Evaluation of Nitrous in the Gas Mixture for Anaesthesia
IEAC	Independent Endpoints Adjudication Committee
mITT	Modified Intention-To-Treat
mBPI	Modified brief pain inventory
mBPI-sf	Modified brief pain inventory- short form
MI	Myocardial infarction
NDS	Non-diabetic stratum
NHMRC	National Health and Medical Research Council
NRS	Numerical rating scale
PACU	Post-anaesthesia care unit
PE	Pulmonary embolus
PI	Principal Investigator
PONV	Postoperative nausea and vomiting
QoR-15	Quality of recovery -15 item questionnaire
SAE	Serious Adverse Event
SD	Standard deviation
SSI	Surgical site infection
WHODAS	World Health Organisation Disability Assessment Schedule 2.0, 12 item

Study synopsis

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.(1) Group allocation is stratified by diabetes status and site.

Non-inferiority margin

We chose an absolute non-inferiority margin of 2% which was agreed by the steering committee using the Delphi method. An absolute increase in risk of infection of 2% with dexamethasone 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.

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.

Further details of the trial design are available in the published PADDI protocol paper.(1)

Endpoint Definitions

Primary endpoint

The primary endpoint for the trial is the occurrence of a surgical site infection (SSI) within 30 days of the day of surgery. The SSI definitions employed are those defined by the CDC criteria,(2) 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). For the purpose of the PADDI trial, we will use the classification groupings of Superficial, Deep and Organ space infections. The IEAC-adjudicated occurrence of any one (or more) of these categories of SSI within 30 days of the index procedure constitutes the presence of the primary endpoint.

Secondary endpoints

1. Deep and organ space infections to 90 days in patients receiving prosthetic material during surgery, considered separately.

2. Superficial, deep and organ space infections to 30 days, considered separately

3. Other infections up to 30 days after the index procedure (i.e.urinary tract infections, pneumonia, catheter-related infections and sepsis), considered separately and together . (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 (3)

5. Chronic Post-Surgical Pain (CPSP) at 6 months after surgery using the following metrics:
   (a) The presence of CPSP, 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
   (b) The presence of Pain at 6 months in the area of the index surgery, regardless of presence prior to surgery
   (c) Severity of CPSP (using the adapted mBPI-sf).
   (d) Incidence and severity of neuropathic symptoms and pain (incidence examined as a binary outcome using the Neuropathic Pain Questionnaire, severity quantified using the adapted mBPI-sf).

6. Death or persistent new onset disability for 6 months following surgery. Persistent new onset disability is defined as a 4-point (8%) or greater increase in the 12-item WHODAS 2.0 score compared with baseline (preoperative) score at both 30 days and 6 months.

Tertiary endpoints

1. Any nausea or vomiting postoperatively to 24 hours post-surgery

2. Any antiemetic usage postoperatively to 24 hours post-surgery

3. Nausea (Up to Day 3) –
   (a) 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, on day 3.
   (b) Antiemetic usage in each of these periods.

4. Vomiting (Up to Day 3) –
   Number of vomiting events in PACU, within first 24 hours following surgery post PACU, on day 2 and on day 3.

5. Highest pain score (NRS, 0–10) at rest and on movement in PACU and in the first 24 hours post-PACU

6. Hospital stay: from the start (date, time) of surgery until discharge from acute care facility.

7. CRP concentration – measured on Day 2 postoperatively.

8. Glycaemic control, defined as the maximal changes in perioperative blood glucose from baseline up to day 2 postoperatively,

9. Hypoglycaemic event rates - a hypoglycaemic event being defined as a blood glucose recording less than 4.0 mmol/L.

10. Hyperglycaemic event rates in patients without diabetes - a hyperglycaemic event being defined as a blood glucose recording greater than 10 mmol/L.

11. Rate of insulin use in patients without diabetes

12. Lymphocyte and neutrophil levels - Change in neutrophil-to-lymphocyte ratios from baseline to Days 1 and 2

13. Mortality at 6 months

14. Unexpected reoperation to 30 days

15. Unexpected readmission to hospital to 30 days

Safety Endpoints

- Any of Myocardial infarction/Cerebrovascular accident/Deep venous thrombosis/Pulmonary embolism
- Serious adverse events and severity of adverse events (mild, moderate, severe), classified by organ system

Randomisation

After written informed consent, patients will be randomised shortly before the induction of anaesthesia. A computer-generated list, accessed by a web-based randomisation service allocated the patient (1:1) to either Dexamethasone or Control group, using a randomisation stratified according to site and known diabetic status of the patient using random permuted blocks.

Statistical criteria for non-inferiority and harm

The primary endpoint of surgical site infection endpoint will be analysed using the modified ITT population with two-sided asymmetric confidence intervals (defined below). Non-inferiority will be declared if the upper endpoint of the confidence interval for the difference in infection rates (Dexamethasone minus placebo) is less than 2%. Harm will be declared if the lower endpoint of the confidence interval lies above 2%.

Interim Analyses

Interim analyses for assessment of non-inferiority and harm of the primary endpoint will be performed after enrolment and 30 day follow up of 1/3 and 2/3 of the total number of patients. These analyses will use two-sided repeated asymmetric confidence intervals. The upper endpoint of the confidence interval for consideration of non-inferiority will be based on the O'Brien-Fleming spending function. The lower endpoint of the confidence interval for consideration of harm will be based on the less conservative Power function with parameter 2. The confidence interval 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 boundaries (Z-values) will be adjusted according to the actual number of patients randomized at the time of each interim analysis.

Should the result cross a designated boundary (i.e. non-inferiority or harm) at an interim analysis, consideration will be given by the DSMC to terminate the trial if the committee believes the interim results are sufficiently compelling to change practice around the world.

Sample size

Sample size calculations for this non-inferiority trial are based on a null hypothesis of Ho: p2–p1 >delta (i.e. 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.(4) Infection rates up to 25.4% have been observed in higher risk cohorts. (5) 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), a numerical simulation assessment with 20,000 replications indicated that, with 4303 completed patients per intervention arm (up to a simulation standard error 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 Dexamethasone 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 Dexamethasone arm, representing clear harm, the probability of falsely declaring non-inferiority is <0.1%, and the probability of (correctly) declaring harm is 83%.

STATISTICAL ANALYSES

General principles

The analysis and reporting of the results will follow the CONSORT guidelines.(6) Baseline characteristics will be tabulated by using appropriate summary statistics.

Data for the primary endpoint will be analysed using each of the modified intention-to-treat (mITT), per protocol (PP) and as-treated (AT) populations (see definitions and details below), with the mITT analysis regarded as the principal analysis. All secondary and tertiary endpoints will be analysed using the mITT population only.

Interpretation of the primary endpoint will be based on confidence intervals. For secondary and tertiary endpoints two-tailed P-values will be reported in addition to confidence intervals. A nominal 5% significance level will be employed.

Apart from adjustment for the multiplicity of interim analyses of the primary endpoint, no other correction for multiple testing will be performed.

Analysis Populations

A. Modified ITT (mITT) population

The mITT population will consist of all randomised patients who undergo induction of anaesthesia and eligible surgery (surgery 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). The mITT 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 under general anaesthesia on the scheduled date
b) patients who withdrew consent prior to surgery
c) clinician refusal at the time of surgery
d) duplicate randomisation
e) study drug not available at the time of surgery
f) screening failures

Patients whose consent is withdrawn post-operatively will have their data used up until the time of withdrawal.

B. Per Protocol (PP) population

The 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.

C. As Treated (AT) population

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 received dexamethasone as randomised
   2. their randomisation is ignored (over-ridden) and they received an initial dose of open-label dexamethasone (or other glucocorticoid)
   3. they received 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 were randomised to placebo and receive placebo, and did not receive open label dexamethasone (or other glucocorticoid) at any time
   2. They were randomised to dexamethasone but do not receive it initially, and did 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.

Primary endpoint analysis – 30 day Surgical Site Infection

mITT analysis

The absolute difference in 30 day infection rates will be summarised with a two-sided, asymmetric confidence interval, adjusted for multiplicity of interim analysis assessments as described above to preserve an overall 95% confidence level. This will be performed using binomial regression with an identity link function to estimate the risk difference, adjusting for diabetic status at time of randomisation. As stated above, non-inferiority will be declared if the confidence interval for the difference in infection rates (dexamethasone – placebo) lies entirely below the non-inferiority margin of +2%. As per CONSORT recommendations, a risk ratio and CI will also be presented, using an analysis using binomial regression with a logarithmic link function.

The main sensitivity analyses for the impact of missing primary outcomes will involve imputing outcomes under “worst-best” and “best-worst” case scenarios (7). In the “worst-best” scenario, a “worst” outcome event (30 day infection) is assigned to all patients missing the outcome in one treatment group, and a “best” outcome event (no infection) is assigned to all patients missing the outcome in the other treatment group. The “best-worst” scenario is the exact opposite assignment of outcomes. Data with the best-worst and worst-best imputed outcomes will be analysed, confidence intervals calculated, and the variation between the resulting two confidence intervals will indicate the range of uncertainty in

results due to missing outcome data. These confidence intervals will scale the standard error from the regression models with the imputed data by dividing by the square root of one minus the overall fraction of missing outcomes as a conservative measure to avoid false precision from the imputed data. If no substantively different conclusions arise from these two analyses then no further missing data assessments will be performed for the primary outcome. If a substantively different conclusion arises then the primary mITT analysis will be repeated using more detailed imputation, specifically multiple imputation with chained equations with 20 imputations, separately for each treatment arm, incorporating information from non-missing baseline and post-baseline variables in the imputation models.

Additional sensitivity analyses will adjust for the stratification variable of study site using binomial regression models with identity link (for risk difference) and with logarithmic link (for risk ratio) incorporating random effects for site using the *gllamm* command in Stata. In the case of convergence difficulties, a random effects logistic regression model will be fit, followed by integration over the random effects to obtain the marginal outcome proportion in each arm (using the *margins* command), and then applying the delta method to calculate the 95% CIs for the risk difference and risk ratio and their P-values (using the *lincom* and *nlcom* commands, respectively).

Further sensitivity analyses will make post-hoc adjustment for any variables exhibiting substantial imbalance across treatment arms at baseline.

Per Protocol analysis

The PP analysis will use the same methods as the mITT analysis, confined to the patients meeting the per protocol population definition.

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 and risk-ratio regressions. Should either regression model fail to converge, a linear model with identity link or Poisson model with logarithmic link (respectively) and robust standard errors will be employed.

As Treated 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 rather than the classification at the time of randomisation will be used in the analysis.

As with the PP analysis, 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 and risk-ratio

regressions. Should either model fail to converge, a linear model with identity link or Poisson model with logarithmic link (respectively) and robust standard errors will be employed.

*True diabetic status is defined as the status recorded at baseline, but with reported non-diabetic patients with a blood glucose level ≥ 11.1 mmol/L and HbA1c > 6.4% reclassified as being diabetic.

Secondary and tertiary endpoint analyses

Secondary and tertiary endpoints will be compared across dexamethasone and placebo arms analyses using a complete case analysis in the mITT population with regression models adjusting for diabetic status at time of randomisation. Binary endpoints (Secondary #1 [S1], S2, S3, S5(a), S5(b), S6, Tertiary #1 [T1], T2, T3(b), T9, T10, T11, T13, T14, T15) 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 5. Death or new disability (S6) requires the baseline, 30 day and 6 month WHODAS measurements all to be present, otherwise the endpoint (for non-deaths) will be set to missing. Patients missing one item in the WHODAS or QoR-15 (S4) scales at any time point will have the value of the missing item imputed as the mean of the other items. Patients missing two or more items will have their WHODAS or QoR-15 scores set to missing. Count outcomes (T4) will use Poisson regression with robust standard errors to account for overdispersion. Continuous endpoints (S4, S5(c), S5(d), T3(a), T5, T7, T8, T12) with reasonably symmetric distributions will use linear regression with robust standard errors to estimate differences in means with 95% CIs, with adjustment for the baseline value of the endpoint if available. Heavily skewed continuous endpoints will be summarised with medians and interquartile ranges and with estimated differences between medians and their 95% CIs computed via quantile regression adjusting for baseline values if available. Hospital length of stay (T6) will be tested across arms using the Wilcoxon–Breslow–Gehan test stratified by diabetes status and hazard ratios estimated using Cox proportional hazards regression adjusting for diabetes status, with data censored at 30 days and in-hospital deaths assigned the longest duration of stay. Assessment of the proportionality of hazards assumption will be made using Schoenfeld residuals.

Subgroup analyses

Planned sub-group analyses will assess consistency of differences between Dexamethasone and placebo arms with respect to the primary and secondary endpoints. These will be assessed using regression models with interaction term(s) between the particular subgroup and randomised arm together with the interaction term(s) between the subgroup and diabetes status. The analyses will provide a point estimate and confidence interval for the effect of randomised arm (RR, RD etc) in each subgroup. For the primary endpoint the confidence intervals will use the final Z (boundary) values accounting for the interim analyses of the primary endpoint, while the secondary endpoints will use conventional two-tailed symmetric 95% confidence intervals. For all analyses the P-value for the interaction term between randomised arm and subgroup will be reported. The subgroup variables are:

- Diabetic status (`true' status as defined above)

- 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
    - ASA ≥ 3
    - Diabetes status= Yes
    - BMI ≥ 35
    - Wound status other than "clean"
    - Surgical classification = Gastrointestinal
- 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 [BMI<18.5], normal [18.5 to <25], overweight [25 to <30], obese [30 to <40], super obese [40+]), ASA physical status (1/2, 3, 4), wound classification, smoking status, average intraoperative oxygen concentration during anaesthesia (approximate quintiles), and duration of surgery (approximate quintiles).

Safety endpoint analyses

Safety endpoints will be tabulated by treatment group without statistical tests or confidence intervals.

PUBLICATION PLAN

The principal manuscript will analyse all endpoints apart from the detailed pain endpoints (S5(b), S5(c), S5(d)) and nausea and vomiting quantification (T3, T4). Subgroup analyses will be restricted to assessment for the primary endpoint only. The pain and PONV endpoints will be analysed in separate manuscripts for CPSP and PONV, respectively.

CHANGELOG

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(i) The explicit recategorisation of the 5 CDC SSI categories into 3 categories has been added in the Primary Endpoint definition.

(ii) Clarification of wording that the secondary endpoints of deep infection and organ space infection to 90 days in patients receiving prosthetic material during surgery will be considered individually.
(iii) A “best-worst”/“worst-best” approach to missing data imputation has been added.
(iv) The definition of ‘true diabetes status’ has been added as the status recorded at baseline, but with reported non-diabetic patients with a blood glucose level ≥ 11.1 and HbA1c > 6.4% mmol/l reclassified as being diabetic. This change is relevant for the subgroup analyses for diabetic status, and for the As Treated analyses.
(v) Subgroup category cutoffs for ASA ≥ 3 and for BMI have been added.

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