Glycaemia substudy of PADDI RCT

Statistical analysis plan Version 1.0 2nd November 2023

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DEFINITIONS and ABBREVIATIONS

The perioperative period is defined as the time from anaesthesia induction to day 1 postoperatively (24 hours post surgical incision).

Diabetes classification:

A person was classified in this substudy as having diabetes as per the PADDI study if [1] :

Diabetes if

- Preoperative diagnosis of diabetes
- Pre-operative blood glucose ≥ 11.1 AND preoperative HbA1c > 6.4% in those who self-identified preoperatively as not having diabetes

BGL	Blood glucose level
BMI	Body mass index
CI	Confidence interval
HbA1c	Glycated haemoglobin
PACU	Post acute care unit
POC	Point of care
RCT	Randomised controlled trial

Study synopsis

Study design

As-treated group substudy of the PADDI RCT, restricted to patients meeting the criteria for diabetes.

Study hypothesis

A single dose of dexamethasone given during surgery will not affect perioperative BGL in patients with diabetes.

Primary Objective:

The main objective is to determine whether a single dose of Dexamethasone in patients with diabetes is associated with higher perioperative BGL in comparison to patients with diabetes who did not receive Dexamethasone during surgery.

Secondary Objectives:

1) to determine whether a single dose of Dexamethasone in patients with diabetes is associated with the requirement for supplementary insulin, 2) to determine whether a single dose of Dexamethasone in patients with diabetes is associated with more episodes of hypoglycaemia and 3) to determine whether glycaemia, as measured by baseline HbA1c and perioperative blood glucose changes, influences surgical site infection in patients with diabetes.

Inclusion criteria for this substudy

Patients classified as having 'true' diabetes in the PADDI RCT (N= 1,157)

Exclusion criteria

- Patients without diabetes as determined by `True' diabetic definition
- More than one dose of Dexamethasone given during surgery

- Dexamethasone given in PACU or on day 1 - If no Dexamethasone during surgery and was given Dexamethasone in either PACU or day 1 or one dose in surgery and a further dose in PACU or day 1 was given.
- Missing non-study Dexamethasone information.

Outcome Definitions

Primary outcome

The maximum recorded perioperative blood glucose concentration

Secondary outcomes

1. The maximum change in blood glucose defined as the change in BGL from induction to the maximum BGL during the perioperative period
2. The maximum change in blood glucose from induction to 8-12 hours post study drug administration
3. Highest intraoperative blood glucose value
4. Peak blood glucose value in PACU
5. Blood glucose value 8-12 hours post study drug administration
6. Blood glucose value day 1
7. Proportion of BGL < 4.0 mmol/L during the perioperative period
8. Requirement for supplementary insulin during the perioperative period
9. Supplementary Insulin dosage required during the perioperative period

    - For those who required supplementary insulin during the perioperative period they will be categorised into

        - Single dose of Insulin only
        - Multiple doses of Insulin
        - Insulin infusion

    Patients receiving more than one type of supplementary insulin during the perioperative period they will be categorised into the 'highest' level of insulin they required during the perioperative period

STATISTICAL ANALYSES

General principles

The analysis and reporting of the results will follow the STROBE guidelines. [2] Baseline characteristics will be tabulated by Dexamethasone group using appropriate summary statistics.

A nominal two-tailed 5% significance level will be employed. No correction for multiple testing will be performed.

Analysis Populations

Patients will be categorised into

- No Dexamethasone during perioperative period, which will include those randomised to placebo who did not get any non-study Dexamethasone and those randomised to Dexamethasone who did not get the study drug Dexamethasone.
- One dose only (during surgery) , which will include those randomised to Dexamethasone and received the study drug and those randomised to placebo but received one dose of non-study Dexamethasone during surgery. This will also include those who were randomised to Dexamethasone but did not get the study drug, however non-study Dexamethasone was given during surgery. No other doses of Dexamethasone up to and including day 1.

Primary outcome analysis – maximum blood glucose during the perioperative period

The maximum BGL will be calculated as the maximum of the following blood glucose variables:

1) Highest intraoperative BGL
2) Peak BGL post acure care unit
3) 8-12 BGL hour post induction
4) morning of day 1 BGL

The maximum blood glucose level will be determined from these variables regardless if one or more are missing.

The continuous skewed primary outcome of maximum BGL will be compared between the two groups using a difference in medians together with a 95% confidence interval and p-value, estimated by quantile regression.

The extent of missingness of the primary outcome will be determined together with the characteristics that differ between patients with the primary outcome missing and present. If the proportion of patients missing the primary outcome exceeds 5%, a supplementary analysis using multiple imputation of the missing outcomes (at all time points) using chained equations will be employed using relevant baseline and postbaseline variables in the imputation models that are predictive of the primary outcome, or of the primary outcome being missing, and constructed separately for each group. Patients who withdrew consent for any data to be used will not be included in these imputations. The results of these multiple imputation analyses will be regarded as supplementary.

Secondary endpoint analyses

Secondary endpoints 1 to 6 will be analysed using quantile regression to estimate medians and their 95% CI. Secondary enpoints 3 to 6, which are blood glucose values collected at different time points, will be analysed at their separate time points.

Secondary endpoints 7 – 8 (binary outcomes) will be summarised by their number and percent and will be analysed using log-binomial regression to estimate risk ratios together with 95% CIs. If nonconvergence is encountered, Poisson regression will be used together with robust standard errors.

Secondary endpoint 9 (ordinal outcome) will have categories summarised by their number and percent and will be analysed using ordinal logistic regression to estimate an odds ratio together with its 95% CIs.

The primary and all secondary outcome measures will be adjusted for the baseline variables found to be imbalanced between the two groups. These variables will be determined if there is an absolute value of the standardised difference of > 0.10 between the dexamethasone and the no dexamethasone groups. [3]

Supplementary analysis of secondary outcomes will be undertaken using multiple imputationas previously described.

Subgroup analyses

Planned sub-group analyses will assess whether the differences in the primary outcome and the SSI outcome between Dexamethasone and non-dexamethasone groups vary across the subgroup factors listed below. These will be assessed using regression models with interaction term(s) between the particular defined subgroup and dexamethasone group. The analyses will provide a point estimate and confidence interval for the effect of dexamethasone group (Difference in medians for maximum perioperative BGL and RR for binary outcome SSI) within each level of the subgroup factor and an overall interaction p-value.

1. HbA1c (<7, 7-7.9, and >7.9)
2. Age - quartiles
3. Sex (Male/Female)
4. BMI – (<18.5, 18.5-24.9, 25-29.9, ≥30)
5. Duration of surgery – quartiles

REFERENCES

1) Corcoran TB, Myles PS, Forbes AB, Cheng AC, Bach LA, O'Loughlin E, Leslie K, Chan MTV, Story D, Short TG, Martin C, Coutts P, Ho KM; PADDI Investigators; Australian and New Zealand College of Anaesthetists Clinical Trials Network; Australasian Society for Infectious Diseases Clinical Research Network. Dexamethasone and Surgical-Site Infection. N Engl J Med. 2021 May 6;384(18):1731-1741. doi: 10.1056/NEJMoa2028982. PMID: 33951362.

2) von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008 Apr;61(4):344-9. PMID: 18313558
3) Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009 Nov 10;28(25):3083-107. doi: 10.1002/sim.3697. PMID: 19757444; PMCID: PMC3472075.

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Blood glucose values recorded during study at the following time points

- Pre-op Pathology Tests -instructions: Please document the highest value for each test. Can be lab or point of care POC (finger prick blood test with glucometer by the nurse / clinician
- BGL on induction (in diabetics only)
- Highest intraoperative blood glucose level (in diabetics only)
- Peak BGL in PACU
- BGL (POC) 8 – 12 hours post dose
- BGL day 1 - refer to results of path tests done on morning after surgery – please document highest values

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