**STUDY PROTOCOL PRO FORMA**

## Title

**Dexamethasone to reduce pain, nausea and vomiting, improve mobilisation and reduce hospital stay in hip and knee arthroplasty: a double blind controlled trial**

## Aims

The primary aim of this study is to determine if the use of dexamethasone immediately pre-operatively and on day 1 post hip or knee arthroplasty:

1. reduces length of stay in hospital, by
2. improving immediate post-operative outcomes and recovery for patients (including reduced pain, reduced use of analgesia, reduced nausea and vomiting, improved range of movement and faster regain of independence)

A secondary aim is to look for evidence of adverse events associated with the intervention.

## Hypotheses

We hypothesize that, by reducing pain, nausea and vomiting, and improving mobilisation, the use of peri-operative dexamethasone will significantly reduce length of stay in patients undergoing total hip or knee arthroplasty procedures.

## Background

Dexamethasone is a glucocorticoids with powerful anti-inflammatory characteristics. Immediately after the surgical incision, local and systemic inflammatory, metabolic, hormonal, and immune responses to the surgery are activated as part of the overall “stress response”. With tissue injury, afferent neuronal activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis sets off various cascades of reactions, resulting in the release of ACTH and cortisol within minutes. Cortisol level reaches a maximum at 4-6 hours and it is proportional to the extent of tissue injury. This is allows mobilisation of energy stores as a survival mechanism in the event of injury, and also, to fuel the metabolic needs of the immune system and the healing process ([Desborough, 2000](#_ENREF_2)). It has been suggested that greater cortisol secretion improves recovery due to the dampening of the inflammatory response ([Desborough, 2000](#_ENREF_2)) and perhaps these effects may be augmented with glucocorticoids.

At the site of tissue injury, cytokines, released by activated macrophages, endothelial cells and fibroblasts, play a major role in the inflammatory response (Burton, Nicholson & Hall, 2004). After major surgery, IL-6, the primary stimulus for the acute phase response, is released together with TNF-α and IL-1, and its concentration reaches its maximum level at 24 hours and remains elevated for 24-48 hours ([Desborough, 2000](#_ENREF_2)). Dexamethasone has been shown to decrease levels of acute phase reactants (CRP and IL-6) following hip/knee arthroplasty, and lower levels of IL-6 are correlated with an increased mobility post hip or knee arthroplasty while lower levels of CRP correlate to post-operative pain levels ([Hall, Peerbhoy, Shenkin, Parker, & Salmon, 2001](#_ENREF_4)). It has also been demonstrated that there is a direct inhibitory effect of locally administered steroids on signal transmission in nociceptive C-fibers when hydrocortisone is used ([Salerno & Hermann, 2006](#_ENREF_6)).

Administering an agent such as Dexamethasone at the time of arthroplasty may be beneficial by reducing these responses by virtue of its anti-inflammatory and immunosuppressive effects. The use of Dexamethasone in adult patients undergoing general anaesthesia was the subject of a systematic review of evidence which demonstrated a small but statistically significant reduction in post-operative pain ([Waldron, Jones, Gan, Allen, & Habib, 2013](#_ENREF_9)). There were no increase infection or delayed wound healing, however blood glucose levels were on average higher at 24 hours post-operative. A meta-analysis by Lunn and Kellet ([Lunn & Kehlet, 2013](#_ENREF_5)) in patients undergoing hip and knee surgery, including arthroplasty and arthroscopy, showed a significant pain reduction in patients in the post-operative period in studies administering >10mg Dexamethasone systemically pre-operatively. Backes et al ([Backes, Bentley, Politi, & Chambers, 2013](#_ENREF_1)), used Hydrocortisone IV injection 8mg on induction and 8mg 24 hours later in patients undergoing arthroplasty. Lower pain levels post knee or hip arthroplasty were reported, and thus advancing recovery through improved mood, early mobilisation and increased ambulation and reducing the risk of adverse health effects associated with prolonged bed rest, resulting in earlier discharge and shorter hospital stays. The use of systemic Dexamethasone (>0.11mg/kg) has been found to provide opioid sparing pain-relief, reducing their associated costs and the potential adverse effects arising from opioid use ([Lunn & Kehlet, 2013](#_ENREF_5)). Finally, studies have shown the effectiveness of glucocorticoids in post-operative nausea and vomiting in patients undergoing total joint arthroplasty ([Backes et al., 2013](#_ENREF_1); [Lunn & Kehlet, 2013](#_ENREF_5)) proposing another avenue for improving post-operative recovery and enabling earlier discharge.

The routine use of glucocorticoids has been questioned because of concerns over safety; the primary concern stems from the suppression of the HPA-axis due to chronic glucocorticoid use, resulting in the inability to mount an optimal protective stress response ([Salerno & Hermann, 2006](#_ENREF_6)). Other concerns include osteonecrosis, impaired wound healing, and increased risk of infection ([Salerno & Hermann, 2006](#_ENREF_6)). However, it has been shown that a low dose (<8mg) short term use of glucocorticoids is safe and that the risk of side effects increases proportionately with longer durations and intensity of treatment ([Salerno & Hermann, 2006](#_ENREF_6)). A meta-analysis of seventeen studies, a thousand and eighty one patients found seven infection complications, four in patients receiving glucocorticoids ([Lunn & Kehlet, 2013](#_ENREF_5)). However, due to the diminished likelihood of this complication, a larger study would be needed to determine an increase in infection rates in the group receiving glucocorticoids ([Lunn & Kehlet, 2013](#_ENREF_5)). In regards to wound healing and white blood cell count, have shown a reduction in the number of mononuclear cells, but the numbers of granulocytes e.g. neutrophils, which are responsible for phagocytosis of debris, remain unaffected. For this reason, the use of glucocorticoids pre or post-operatively does not seem to affect wound healing, or increase or mask infection rates (Smith et al, 2006).

For this study, an 8mg dose of Dexamethasone will be given pre-operatively and at 24 hours post-operatively to diminish the peripheral and central inflammatory response by inhibiting production of pro-inflammatory cytokines before surgery ([Lunn & Kehlet, 2013](#_ENREF_5)), with its effects being most apparent in the first 24-48 hours ([Salerno & Hermann, 2006](#_ENREF_6)). An 8mg dose of Dexamethasone has been found to reversibly suppress the HPA-axis for up to a week, but this is clinically benign ([Salerno & Hermann, 2006](#_ENREF_6)).

## Methods

## Design

A double-blinded randomised placebo controlled study design will be used. Participants will be patients undergoing single side total knee or hip arthroplasty at the Launceston General Hospital, the intervention is the administration of two doses of 8mg of dexamethasone intravenously immediately pre-operatively and 24 hours later. Placebo will be normal saline, prepared to be identical in appearance to the interventional drug.

## Setting

This study will take place at the Launceston General Hospital, Department of Surgery.

## Participants

## *Screening*

Potential participants will be identified and screened (Appendix 1– Pre-screening tool) at the pre-admission clinic at the Launceston General Hospital and include patients who are booked for total knee or hip arthroplasty. Pre-admission clinic occurs prior to a planned admission for elective surgery and is an opportunity for patients to be screened for conditions which may impact on their operative suitability and be prepared for surgery with the necessary pre-operative care.

## *Inclusion criteria:*

* People who are presenting to preadmission clinic for single joint hip or knee arthroplasty.
* Able to provide informed consent
* Age 18 years and older

## *Exclusion criteria:*

* Type 1 or type 2 diabetes mellitus; renal failure; hepatic failure
* Use of oral corticosteroids over past 6 months
* Allergic or adverse reaction to corticosteroids in the past
* Allergy to the food preservative Sulfite (this does not include Sulpha containing medications)
* Active peptic ulcer disease with symptoms present in the previous 6 months
* Previous GIT haemorrhage
* Pregnancy and lactation
* Past history of psychotic illness (including psychotic depression)
* Current systemic fungal infection
* Administration of live vaccine in the previous 3 months
* Myasthenia gravis

## *Sample size and justification*

Primary sample size has been calculated based on length of stay, as a key outcome for resource utilisation, and a surrogate outcome of post-operative recovery and hence immediate post-operative patient outcomes.

Using existing data which has been collected by the PI from a previous study in a similar population, in order to detect a 20% reduction in length of stay from an expected value of 6.4 days (SD 2.7) with a power of 80% a sample size of 71 is required for each group. As loss to follow up is not likely to be a significant issue in this study, we will aim for a sample size of 142. The LGH completes approximately four arthroplasy procedures / week. Allowing for non-consent and exclusion criteria, we anticipate the recruitment of 1-2 participants/ week, meaning that recruitment time will be approximately 24 months.

## Study drug

Dexamethasone is a synthetic adrenocorticosteroid with glucocorticoid activity. It is a highly active glucocorticoid, being about 25 to 30 times as potent as hydrocortisone. Dexamethasone has little if any mineralocorticoid activity (Appendix 2 – Product Information).

Dexamethasone’s therapeutic action is as an anti-inflammatory and immunosuppressant. As a glucocorticoid it prevents the capillary dilation and phagocytosis associated with hypersensitivity responses which occur after antigen-antibody reactions. The principal metabolic actions of dexamethasone are on gluconeogenesis, glycogen deposition and protein and calcium metabolism. Dexamethasone also influences the mobilisation, oxidation, synthesis and storage of fats. Dexamethasone suppresses the release of adrenocorticotrophic hormone (ACTH) from the pituitary when used for long periods resulting in inhibition of endogenous corticotrophin secretion.

Except for its use in the treatment of adrenal insufficiency, dexamethasone does not cure disease. Rather, the anti-inflammatory and immunosuppressant actions of dexamethasone suppress the symptoms associated with the disease.

Apart from allergic reactions, its use on one or two occasions is considered to be unlikely to be associated with side effects (Appendix 2 – Product Information). However its potential effect on glucose metabolism, peptic ulcer development, psychotic symptoms, and its immunosuppressive effect are sufficient for us to exclude potential participants who have past or recent history of these conditions or are at risk from immunosuppression (Appendix 1 – Pre-screening tool).

Product information (Appendix 2) and consumer information (Appendix 3) are attached. In light that the proposed use of Dexamethasone is not an expressed use according to product information, this study will proceed under the CTN scheme.

## Recruitment and data collection

Potential participants will be screened for exclusion criteria and provided with verbal and written information about the study at pre-admission clinic. They will be consented at this time, however given there may be unanticipated delays in surgery, consent will be confirmed immediately prior to surgery (ie consent forms will be double signed by the patient). This process should allow us to anticipate the number of participants per week and notify pharmacy of how many packs need to be prepared at the beginning of each week.

## Randomisation

Randomisation and preparation of trial drugs will be conducted by the pharmacy department at the Launceston General Hospital. At the beginning of each week pharmacy will prepare randomisation packs for the number of participants who are booked for arthroplasty that week; this information will be provided to them by the research assistant. Unused randomisation packs will be destroyed at the end of week as they are not able to be kept due to lack of long term stability of the intervention drug, however the randomisation will be re-allocated the following week. The pre-operative intervention drug/placebo will be administered by the anaesthetist and the 24 hour dose will be sent with the patient to the ward where it will be administered by nursing staff 24 hours after the first dose. This dose will be ordered on the patient’s medication chart by the anaesthetist.

## Procedures

**Anaesthesia**

If appropriate for the patient the anaesthetic will be attempted to be standardised as much as practically possible. All patients will receive preoperatively antibiotics that will continue for 24 hours post-surgery. Ultimately however this is a pragmatic study and the anaesthetist can use which ever anesthetic is felt to be the most appropriate for the patient. On induction the dexamethasone or placebo will be given. The anaesthetic guidelines are as follows after consultation with the anaesthetic department at the LauncestonGeneral Hospital.

Spinal Anaesthesia o   0.5% Bupivicaine ( Plain or heavy, dose volume to be at discretion of anaesthetist)

o   Intrathecal fentanyl 15-20mcg

o   NO other intrathecal medication (i.e. no spinal morphine/midazolam/clonidine)

·      Intraoperative sedation with Midazolam +/- propofol infusion

·      Morphine PCA initiated in recovery and to continue for 24h (24h Morphine requirements could be an outcome measure of analgesia)

·      Regular Paracetamol orally, to start post-op and continue to discharge

·      Oral Endone/SC morphine PRN from 24h to discharge

·      Rescue Antiemetic if nausea/vomiting is Ondansetron, other antiemetics can be charted if there is a contraindication to ondansetron, or be available as "second line" agents (Antiemetic given/not given could be an outcome measure)

The following should not be given

·      Major Nerve blocks (femoral, fascia iliaca, sciatic, adductor canal)

·      Prophylactic (intraoperative) antiemetics

·      NSAIDs

·      Long acting oral opioids (Oxycontin/Targin)

·      Tramadol

·      Pregabalin/Gabapentin

Other considerations:

·      Patients already on opioid analgesia should continue these as their "regular" medications in addition to the above analgesia plan. (It would be worth collecting this data however)

·     Enrolled patients in whom spinal anaesthesia is not possible (e.g. contraindication or technical failure) should receive general anaesthesia with propofol infusion.

**Surgical technique**

The TKAs and THRs are performed to the surgeons’ preference.

**Postoperative management**

Postoperative management will be consistent with usual practice. At all times multimodal oral analgesia regime is utilized to achieve satisfactory analgesia in all patients.

**Intervention medication**

24 hours post-surgery the second injection of dexamethasone or placebo is given by the ward nurse, as charted by the anaesthetist.

**Mobilisation and home discharge:**

Patients will be designated as ready to be discharged when they fulfil the following discharge criteria, assessments will be made twice daily – morning and late afternoon. Assessments will be based on patient health records and where necessary (if not documented) the research assistant will enquire with the relevant health carer (Appendix 4 – Readiness for discharge chart):

* Pain controlled with oral medication.
* Patient can get in and out of bed and to the toilet without assistance.
* Physiotherapist has deemed patient can mobilise safely independently.
* Physiotherapist has deemed patient can mobilise safely on steps.
* Occupational therapist is happy for patient is safe to return home.
* Medical staff deem patient is medically stable for discharge.

This will be documented by the researcher based on the care management plan and health records. The actual discharge date will also be noted, any reason for a delay in discharge will be noted.

## Data collection and measures (see Appendices 4 & 5)

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| **Booking visit (Consultant):*** Suitability for joint replacement confirmed and decision to place on waiting list made
* Research assistant notified of patients name, alerted when booked for surgery and pre-admission clinic
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| **Pre-admission clinic (Research assistant)**:* Eligibility screening
* Information provided, consent obtained
* Patient advised that consent can be withdrawn at any time, and that consent will be confirmed prior to surgery
* Baseline data collected: Age; Gender; Street number and name;
* Site and type of planned operation
* Past medical history; Previous arthroplasty
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|  |
| **On day of surgery (Research assistant)*** Consent confirmed
* Baseline glucose (should be fasting) If greater than 7 🢥**exclude from study**
* Baseline measures of pain (VAS) and nausea (VAS)
* Baseline measure of mobility (Timed up and go)
* Participant randomised according to concealed allocation packs provided by pharmacy to theatre

**On day of surgery (Anaesthetist)*** Dexamethasone/Placebo administered pre-operatively
* Second dose of dexamethasone/placebo ordered on patient’s medication chart
* Allocation pack returned to ward with patient for administration of second dose

**24 hours post-operation*** Second dose of Dexamethasone /Placebo administered
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| **Post-operative measures*** Data extracted from patient chart and clinical pathway regarding pain and pain management, management of nausea and vomiting, evidence of complications.
* Timed get up and go test will be performed daily when patient is able to comply
* QID glucose until 24 hours after second dose of dexamethasone
* Pain and nausea (visual analogue scale) will continue to be measured twice daily throughout admission
* Readiness for discharge instrument will be applied morning and afternoon (appendix)
	+ Pain controlled with oral medication.
	+ Patient can get in and out of bed without assistance. To toilet
	+ Physiotherapist has deemed patient can mobilise safely independently.
	+ Physiotherapist has deemed patient can mobilise safely on steps.
	+ Occupational therapist is happy for patient is safe to return home
	+ Medical staff deem patient is medically stable for discharge.
* Date of discharge
* Participants will be asked at discharge: “How satisfied (on a scale from 1-10) were you with your recovery immediately after surgery”
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|  |
| **Post-discharge*** Participants will be followed up by phone at 6 weeks post operation to determine whether there were any complications of surgery in the 6-week period post discharge. Participants will also be asked how satisfied they were (Likert scale 1-10) with their recovery – while in hospital; in the days after hospital, and in the weeks after discharge.
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**Data analysis**

The adequacy of randomisation will be tested by comparing the distribution of potential confounding variables in the steroid and placebo groups: age, gender, proxy SEIFA, baseline pain, nausea, mobility etc. This will be performed using general linear modelling, ordered logistic regression and logistic regression for continuous, ranked and binary data respectively. Any deviations from even distributions will result in inclusion of those variables in the multivariate primary outcome analysis.

The primary outcome of LOS (as judged by time from admission to readiness for discharge) will be compared will be compared using mixed effects linear regression and/or mixed effects ordered logistic regression. The choice will depend on whether and the degree of any deviations from the tested assumptions of linear regression. The raw results will be displayed for illustrative purposes, but either box-cox transformed or logarithmically transformed LOS (if log transformation is adequate to correct assumption violations) will be used to test the hypothesis. Mixed effects ordered logistic regression will be used to test the hypothesis if transformation fails to correct the assumption violations. In each case, adjustment for potentially confounding variables will be included in the analysis.

Secondary outcomes of post-operative pain, nausea and mobility will be analysed using mixed effects linear regression and/or mixed effects ordered logistic regression as described for the primary outcome, corrected for repeated measures and multiple comparisons, and adjusted for potentially confounding variables. Although VAS scales are conventionally analysed using “parametric” statistical tests, they are actually inherently rank-ordered, since they are not constructed to be of equal value per unit of measurement across their entire range. Therefore all linear regression results will be checked using ordered logistic regression analysis to verify that assumption of linearity. Nevertheless, the results will be presented as linear analysis for purposes of comprehensibility.

**Safety Considerations**

Dexamethasone is a drug which is commonly used for a variety of conditions. Most of the risks associated with dexamethasone occur as a result of long term use. Given that participants are only receiving two doses of Dexamethasone and the dose is relatively small, the risks are small. However there are complications which can result from the short term exposure to dexamethasone. These are:

* Temporary increase in blood sugar levels
* Peptic ulceration
* Immune suppression
* Psychiatric disturbance
* Impaired or delayed wound healing or wound infection

Patients with diabetes, a recent history of peptic ulceration, a history of bleeding from a peptic ulcer, a current infection or recent live vaccine that may be impacted by immunosuppression, and a history of serious psychiatric disturbance will be excluded from the study.

Blood glucose levels will be monitored until 24 hours after the last dose of dexamethasone.

Reduced blood flow to bone, causing avascular necrosis (death of bone) to the humeral/femoral head is a rarely reported serious side effect, with all reports in the literature associated with very high dose or long term use of Dexamethasone ([Fast, Alon, Weiss, & Zer-Aviv, 1984](#_ENREF_3); [Talamo et al., 2005](#_ENREF_7); [van Schaardenburg, van den Brink, & Wieringa, 2001](#_ENREF_8)).

Adverse events will be reported to the primary investigator and reviewed by the primary investigator and if deemed serious and potentially related to the intervention referred to an independent Clinician at the LGH (Dr Anne Corbould, endocrinologist) who will review the event and determine its significance related to the study.

A priori adverse events to be recorded are:

1. Infection (any diagnosis of infection resulting in any treatment)

2. Avascular necrosis.

3. Death (including cause and likelihood of any causal link between treatment or study participation and death)

Backes, J. R., Bentley, J. C., Politi, J. R., & Chambers, B. T. (2013). Dexamethasone Reduces Length of Hospitalization and Improves Postoperative Pain and Nausea After Total Joint Arthroplasty: A Prospective, Randomized Controlled Trial. *The Journal of Arthroplasty, 28*(8, Supplement), 11-17. doi: <http://dx.doi.org/10.1016/j.arth.2013.05.041>

Desborough, J. P. (2000). The stress response to trauma and surgery. *British Journal of Anaesthesia, 85*(1), 109-117. doi: 10.1093/bja/85.1.109

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Lunn, T. H., & Kehlet, H. (2013). Perioperative glucocorticoids in hip and knee surgery – benefit vs. harm? A review of randomized clinical trials. *Acta Anaesthesiologica Scandinavica, 57*(7), 823-834. doi: 10.1111/aas.12115

Salerno, A., & Hermann, R. (2006). *Efficacy and Safety of Steroid Use for Postoperative Pain Relief* (Vol. 88).

Talamo, G., Angtuaco, E., Walker, R. C., Dong, L., Miceli, M. H., Zangari, M., . . . Anaissie, E. (2005). Avascular necrosis of femoral and/or humeral heads in multiple myeloma: results of a prospective study of patients treated with dexamethasone-based regimens and high-dose chemotherapy. *J Clin Oncol, 23*(22), 5217-5223. doi: 10.1200/jco.2005.11.676

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Waldron, N. H., Jones, C. A., Gan, T. J., Allen, T. K., & Habib, A. S. (2013). Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. *British Journal of Anaesthesia, 110*(2), 191-200. doi: 10.1093/bja/aes431