Analgesia following LNG-IUS insertion, a randomised controlled trial: vaginal Diazepam vs placebo.

Project Team Roles & Responsibilities

**Principal Investigator**

* Dr Emma Readman, Director of Endosurgery B Unit
	+ Mercy Hospital for Women

**Associate Investigators**

* Dr Madeleine Smith
	+ Project Coordinator
	+ Responsible for recruitment, data collection and analysis
* Dr Lauren Hicks, Endosurgery Fellow
	+ Project creation, recruitment and review of publication
* Dr Lenore Ellett, Director of Endosurgery A Unit
	+ Direction in study design and preparation for publication
* Dr Samantha Mooney, Consultant Gynaecologist
	+ Project creation, recruitment and review of publication

Background

Levonorgestral-releasing intrauterine devices (LNG-IUS), such as the Mirena (Bayer), are being increasingly prescribed in Australia(1). Despite their proven efficacy in contraception(2), heavy menstrual bleeding(3) and pelvic pain(4), overall population usage remains low. One of the contributing factors to this is thought to be fear around pain with and following IUD insertion(5). 59% of nulliparous women reported moderate to severe pain in the first 24 hours following LNG-IUD insertion, reducing to 31% from 24-72 hours(6). Cramping after IUD insertion has been reported to be the main cause for IUD discontinuation in the first 6 months after placement(7). Studies assessing possible methods to reduce post-insertion pain have shown mixed results(8). Misoprostol insertion may reduce pain with insertion, however it causes increased pre-insertion cramps and no difference in cramping 24 hours post insertion(9). NSAIDs have been shown to be beneficial in the management of post-insertion pain(10).

Vaginal administration of diazepam has been proposed as a treatment for pelvic floor muscle spasm(11, 12) and is recommended for this indication by the Pelvic Pain Foundation of Australia. Diazepam acts as a muscle relaxant and vaginal route of administration prolongs the half-life(13) while allowing local administration. Oral preparations are currently being evaluated (clinicaltrials.gov), however, to our knowledge, no data exists on the impact of vaginal Diazepam administration following IUD insertion.

Our aim is to evaluate the impact of a dose of vaginal diazepam following insertion of the Mirena IUD in an outpatient setting on pelvic pain and cramping. We hypothesize that patients will experience a reduction in post-insertion pain compared to placebo.

Project Design

Double-blinded, placebo-controlled, randomized controlled trial

**Site**

Mercy Hospital for Women, Heidelberg

**Intervention arms**

* Insertion of 10mg vaginal diazepam pessary or identical placebo immediately following LNG-IUD placement in an outpatient setting

**Randomisation**

* 1:1 randomisation to active and placebo treatment with stratification based on parity (nulliparous vs multiparous)

**Participants**

Women undergoing elective outpatient insertion of LNG-IUS

* Inclusion Criteria
	+ Premenopausal
	+ Nulliparous or multiparous
	+ Availability of carer to drive patient home from appointment
	+ Access to a computer and email account for completion of questionnaires
	+ Written English language proficiency to provide consent and complete questionnaires
* Exclusion Criteria
	+ Allergy or contraindication to diazepam or pessary components
	+ Contraindication to outpatient insertion of IUD
	+ Postnatal <6/52 or breastfeeding

**Sample size calculation**

* Sample size calculations have been based on the reported incidence of pain at 24 hours following IUD insertion reported by Hall et al 2016. They used a 4-point pain scale at this time point (no pain, mild pain, moderate pain, severe pain).
* We plan to use a 5-point pain scale (no, mild, moderate, severe, extreme) in our data collection
* Sample size required to detect a reduction in primary outcome by one third (from 59% to 39%), with 80% power and 0.05 type 1 error
	+ 97 participants in each group, 194 total
	+ Aim to recruit 120 participants in each group to allow for loss to follow-up

**Recruitment**

* Patients booked for an outpatient LNG-IUD insertion will be approached for participation
* A phone-call will be made by a member of the research team informing the patient of the study and gauging interest in participation
* This phone call will occur at least 1 week prior to the scheduled appointment
* If the patient agrees to participate in the study a PCIF form will be sent via email to the patient through the red cap data base system



**Script for Phone Contact**

I am a doctor/nurse from the Mercy Hospital for Women contacting you on as you have been booked for an outpatient Mirena insertion and have indicated that you may be interested in participating in a research project.

Before we begin would you mind confirming your full name, date of birth and address?

Our research team are looking at trialling a new medication to manage pain post insertion of Mirena, in the hope that in the future we can make awake Mirena insertion a more comfortable process for all women. Is this something you are interested in hearing more about?

In order to be included in this study you should no longer be breast feeding and would need someone to drive you home following the procedure. You will also need to have access to an email account so that we are able to contact you easily following your Mirena insertion.

This medication used in this study is called diazepam and is usually used as a tablet to treat muscle spasm pain. The aim of the research project is to see weather using this medication reduces the cramping some women experience after Mirena insertion. Common side effects of this medication include drowsiness and light-headedness.

As part of this research study participants would receive a vaginal pessary as part of the Mirena insertion process. This pessary will contain either diazepam or a placebo. Neither you nor the doctor will know if placebo or diazepam has been administered at the time. The pharmacy will be aware which medication has been given and can provide this information to your doctor if needed. This will not significantly prolong the length of the procedure.

Study participants will then be contacted via email and asked to complete a short questionnaire regarding pain levels at day 1, day 3 and day 7 following insertion.

If this is something you would be interested in participating in, or would like to hear more about, I can email you a document with more detailed information. After carefully reading through this information, if you would like to participate you will need to complete and return a consent form.

**COVID Safe Plan**

* Adherence to Hospital based COVID protocols
	+ As applicable at time of patient contact (Note these may vary from current protocols)
		- Patient screening at presentation to hospital
		- Use of surgical masks by both doctor and patient
		- Limiting presence of a support person when possible
* Intervention should not prolong time of patient/doctor contact
	+ This study does not require any additional hospital visits or clinician contact beyond what is required for medical care
	+ Recruitment for study will occur via phone contact
	+ Consent process should be completed prior to patient presentation to hospital if possible. Where not possible, there will be no additional hospital visit required
	+ Follow up via telehealth/email contact

**Data collection** (participant commitment, duration and follow-up):

* Time-points
	+ Day of LNG-IUD insertion
		- Baseline data collection including patient demographics, reason for insertion, pre-insertion pain assessment
		- Post-insertion questionnaire assessing experience of insertion
	+ Day 1 post-insertion
		- Email to patient
			* Questionnaire to assess pain in first 24 hours following insertion and any adverse effects from treatment
			* Estimated time to complete: 10 minutes
	+ Day 3 post-insertion
		- Email to patient
			* Questionnaire to assess pain in 24-72 hours following insertion and any adverse effects from treatment
			* Estimated time to complete: 10 minutes
	+ Day 7 post-insertion
		- Email to patient
			* Questionnaire to assess pain in first week following insertion and any adverse effects from treatment
			* Estimated time to complete: 10 minutes
		- Follow-up phone call if no/incomplete response to day 3 and 7 questionnaires
	+ 3 Months post-insertion
		- Routine clinic review
		- Questionnaire to assess patient satisfaction and discontinuation rate (can be provided via email if in-person review does not occur)

**Data Collection and Storage**

* Demographic data will be collected from patient medical records at the Mercy Hospital for Women and patient questionnaire
* Assessment immediately following insertion will be collected via paper-based questionnaire
* Patient email questionnaires will be administered via REDCap online database management software
* All collected data will be securely stored on MHW servers using the REDCap system

**Data analysis**

* Data will be analysed with the assistance of a trained statistician
* Pre-defined subgroup analyses of indication for LNG-IUD insertion (pelvic pain or dysfunctional uterine bleeding) and parity are proposed

**Outcome measures**

* Primary outcome: Moderate, severe or extreme pain in first 24 hours after LNG-IUD insertion
* Secondary outcomes:
	+ Median pain scale response in first 24 hours post-insertion (using non-parametric analysis of ordinal data)
	+ Moderate, severe or extreme pain 24-72 hours post-insertion
	+ Worst pain in 1 week following insertion
	+ Discontinuation rate at 3 months’ following insertion
	+ Adverse effects of treatment

**Investigational Drug**

* Diazepam
* Manufacturer: Healthsmart Pharmacy and Compounding Parkville
* Approved therapeutic indications: anxiety disorder, alcohol withdrawal, muscle spasm, spasticity, athetosis
* Mode of action: activation of gamma-aminobutyric acid resulting in anxiolytic, sedative, muscle relaxant and anticonvulsant effects
* Dosage regime: 10mg vaginal pessary as single dose
* Excretion: Primarily urinary excretion of metabolites
* Contraindications: Hypersensitivity to benzodiazepines, COPD with respiratory failure, severe respiratory insufficiency, sleep apnoea, myasthenia gravis, CNS depressant dependence
* Adverse effects: sedation, fatigue, muscle weakness, ataxia, tolerance/dependence with prolonged use
* In line with TGA requirements, patients recruited will have a script for the trial drug or placebo faxed to the manufacturer. Randomisation will be performed using randomizer.org, with stratification for parity, and the appropriate blinded medication will be posted to the hospital for administration after Mirena insertion

Results, Outcomes and Future Plans

**Dissemination of results**

* To participants
	+ Participants will not be routinely unblinded at the completion of the study
	+ Participants with a serious adverse event will be immediately unblinded
	+ Participants may contact the study coordinator after completion of the study if they wish to know their treatment group
* Publications
	+ Results for this study are planned to be submitted to a peer-reviewed journal
* Follow-up research
	+ The participant cohort may be approached for further research at 5 years after insertion to assess for long-term LNG-IUD discontinuation rate

References

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