Local anaesthetic infiltration in rubber band ligation of rectal haemorrhoids: study protocol for a three-arm, double-blind randomised controlled trial (PLATIPUS trial)

Eleanor G R Watson, Kirby R Qin, Philip J Smart, Adele N Burgess, Helen M Mohan, David M Proud

INTRODUCTION
Background and rationale
Haemorrhoids are the most common anorectal condition in Western countries, affecting up to 40% of the population. They occur when prolonged increases in abdominal pressure cause outpouching of physiologic anal vascular cushions. The major risk factors for the development of haemorrhoids are chronic constipation and straining with defecation, but the condition is also associated with pregnancy, obesity, chronic cough and ascites. Internal haemorrhoids, which occur above the dentate line, typically present with painless rectal bleeding and itch. Below the dentate line, external haemorrhoids can present like internal haemorrhoids, but can also cause pain if they become thrombosed or incarcerated.

Several options are available for the management of haemorrhoids. First-line therapy involves lifestyle modifications including a high fibre diet, increased fluid intake and regular exercise. Glycerol trinitrate, nifedipine or topical local anaesthetics (LA) can be used for symptom relief. Second-line therapy involves non-operative treatments including rubber band ligation (RBL), sclerotherapy and infrared coagulation. Of these options, RBL is the most common as it is effective, relatively simple, associated with minimal complications and can be performed as a day procedure in the outpatient setting. Third-line therapy involves surgical management, such as excisional or stapled haemorrhoidectomy.

RBL involves placing a band on the mucosal aspect of an internal haemorrhoid, causing ischaemia, necrosis and sloughing of the tissue.

METHODS AND ANALYSIS
This is a multicentre, prospective, three-arm, double-blind randomised controlled trial of adults booked for haemorrhoid banding. Participants will be randomised to one of three groups in a 1:1:1 ratio: (1) submucosal bupivacaine injection; (2) pudendal nerve ropivacaine injection and (3) no local anaesthetic. The primary outcome is patient reported postprocedural pain (scored 0–10) from 30 min to 2 weeks. Secondary outcomes include postprocedural analgesia use, time to discharge, patient satisfaction, time to return to work and complications. A sample size of 120 patients is required to achieve statistical significance.

Ethics and dissemination
This study received Human Research Ethics Approval from the Austin Health Human Research Ethics Committee (March 2022). Trial results will be submitted to a peer-reviewed journal, and presented at academic meetings. A summary of the trial results will be made available to study participants on request.

Trial registration number
ACTRN1262200006741p.
theory, the procedure should cause minimal-to-no pain as bands are placed above the dentate line, which has minimally senesce visceral innervation. Yet, pain is the most common side effect of RBL, affecting up to 90% of patients and typically worst in the first 24 hours postprocedure. At many institutions in Australia, it is standard practice to administer LA in RBL. The reasons for pain following this procedure are not well defined. Possible explanations include incorrect band placement below the dentate line; spasm of the anal sphincter muscles; patients reporting visceral sensations of distension or dragging as pain; and the relatively gradual transition from somatic to autonomic innervation at the dentate line causing somatic nerves to still be stimulated by the procedure. Last describes the indistinct line of change from gut to skin mucosa at the dentate line, in contrast with the abrupt change from squamous to columnar epithelium at the gastro-oesophageal junction.

Currently, there is a lack of evidence around the best analgesic strategy in patients undergoing RBL. In practice, patients may receive a submucosal injection of LA at the banding site, a pudendal nerve block (PNB), or neither, with the choice largely dependent on the individual proceduralist. Randomised studies of submucosal LA report varying efficacy. Results from a recent comparative cohort study by Behrenbruch et al suggest that submucosal LA reduces periprocedural analgesic requirement and time to discharge, however, this study was not randomised and may have been subject to bias. PNB is well researched in the context of surgical haemorrhoidectomy, and is considered best practice, but its efficacy in RBL has not been examined.

Objectives
There is a need for high-quality research to identify the optimal analgesic regimen for patients undergoing RBL for haemorrhoids. The aim of this study is to compare the effectiveness of submucosal LA, PNB and routine analgesia alone on postprocedural pain, analgesic use, time to discharge and patient satisfaction.

Additional cost-effectiveness analyses will be undertaken to assess the impact of these interventions from a healthcare expenditure perspective. If there is no significant treatment effect, cost-minimisation analyses will be performed.

Trial design
This is a multicentre, prospective, three-arm, double-blind, randomised controlled trial of adults receiving RBL for haemorrhoids. Participant recruitment and data collection is anticipated to take place from April 2022 to April 2023, with data analysis expected to be complete by June 2023.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting
This study is planning to recruit adults (18 years and above) at multiple public and private hospitals across the states of Victoria and Tasmania, Australia. RBL and anaesthetic interventions will be performed in operating theatres and endoscopy suites by colorectal surgeons.

Eligibility criteria
Patients are eligible for this study if they are aged 18 years or older and undergoing RBL of haemorrhoids. Exclusion criteria are as follows: (1) previous reaction to the LA agents used in this study (ie, ropivacaine, bupivacaine); (2) additional anorectal conditions (eg, Crohn’s disease anal fissure) or (3) receiving RBL in conjunction with another major interventional procedure. Patients will remain eligible if they undergo minor interventional procedures (eg, polypectomy) or non-interventional procedures (eg, colonoscopy).

Interventions
This is a three-arm trial comparing submucosal LA infiltration, PNB and standard care for analgesia in haemorrhoid banding. Participants in the submucosal LA group will receive 1–2mL of 0.5% bupivacaine with epinephrine (1:200 000) 2.5mg/mL injected in the submucosal plane just proximal to the placement of the rubber band, intraprocedure, immediately prior to placement of the band. Participants in the PNB group will receive 20mL ropivacaine 1% 10mg/mL injected at the pudendal nerve on the ipsilateral side of the haemorrhoid to be banded, administered using anatomic landmarks, intraprocedure, immediately prior to placement of the band (if haemorrhoid disease is bilateral, then the block will be administered bilaterally). To standardise technique, the nerve block will be administered with the aid of an instructional video, which will be distributed to all participating proceduralists. All proceduralists will be consultant surgeons experienced in the administration of LA in colorectal procedures. Participants in the standard care group will receive no LA injections. All participants will have access to routine intraprocedural and postprocedural systemic opioid and non-opioid analgesia, administered via the intravenous or oral route, by either the treating anaesthetist, nursing staff or patient, as appropriate.

All of these interventions are routinely used at the participating study sites in RBL procedures. The decision to opt for one analgesic strategy over another for an isolated RBL procedure in the population eligible for this study is proceduralist dependent; therein lies the clinical equipoise for this study. Accordingly, this trial does not involve the use of unapproved therapeutic goods.

Outcomes
The primary outcome measure of this study is patient-reported pain scores at 30 min, 2 hours, 4 hours, 24 hours and 2 weeks postprocedure. Pain scores will be assessed using the Numerical Rating Scale, which asks patients to rate their current level of pain as an integer on a scale of 0–10, with 0 being ‘no pain’ and 10 being ‘worst possible pain’. This scale is used extensively in clinical and research settings and has been validated as a sensitive and reliable measure of pain.
The early time points have been chosen based on the known trajectory of postprocedure pain in RBL and the duration of action of the LA agents used in the interventions. An additional time point of 2 weeks has been included as it is important for clinicians to understand patients’ overall satisfaction with their procedure outside of the immediate postprocedural period.

Secondary outcome measures are: use of postprocedural systemic opioid and non-opioid analgesia in recovery prior to discharge; time to discharge; overall satisfaction with the haemorrhoid banding procedure and postprocedural days until return to work or usual activities.

Complications following the procedure will also be assessed. Complications include those outlined by the European Society for Coloproctology Core Outcomes Set; incontinence, abscess, retention anal stenosis and fistula. Additional relevant complications defined by previous systematic reviews will also be assessed, including syncope and rectal bleeding.

Sample size
A sample size of 40 participants in each group, 120 in total, is required to achieve a clinically significant reduction in both postprocedural pain score and opioid use.

Based on meta-analysis comparison of PNB versus routine analgesia/control after surgical haemorrhoidectomy by Mongelli et al, we anticipate a pain score reduction of 3 ± SD 2.5 (out of 10) and an opioid-use reduction from 65% to 22% of participants. We also conservatively predicted that pain score reduction after submucosal LA would be half that of PNB (ie, 1.5 ± SD 2.5). Therefore, to achieve pain score reductions of 1.5 ± 2.5 (submucosal LA vs control) and 3 ± 2.5 (PNB vs control), 32 and 10 participants would be required in each group, respectively. Calculations are based on 90% power at a 5% level of significance (b = 0.1, a = 0.05). Groups were made equal with 32 participants each (96 total) and increased to 40 each to allow for 25% participant withdrawal and lost to follow-up.

Recruitment
Eligible participants will be identified by investigators via theatre booking lists, where patients are documented as being booked for RBL.

METHODS: ASSIGNMENT OF INTERVENTIONS
Allocation sequence generation, concealment and implementation
A randomisation sequence will be prospectively generated with online software (sealedenvelope.com), using permuted blocks with an allocation ratio of 1:1:1. An independent investigator not involved in other study activities will document the sequence in sequentially numbered, opaque sealed envelopes. When investigators recruit participants, they will attach a sealed envelope to the RBL procedure consent form. Just prior to the procedure, the proceduralist will open the envelope to determine which intervention needs to be administered (if any) alongside the RBL procedure.

Blinding
Investigators involved in recruitment, data collection and analyses will be blinded to the permuted block sizes and participant group allocation. Participants will also be blinded to their group allocation. Proceduralists will not be blinded to study groups, but will not be involved in study activities other than administering the study intervention(s).

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS
Data collection methods
To address the primary objective of the study, we will collect patient-reported pain scores. Participants will be asked by researchers to rate their pain in recovery. After discharge, pain scores will continue to be collected using follow-up phone calls.

To address the secondary objectives of the study, we will collect data on: participant use of paracetamol, non-steroidal anti-inflammatories and opioids in recovery prior to discharge; time to discharge; overall participant satisfaction with the haemorrhoid banding procedure; postprocedure days until return to work or usual activities; and procedure associated complications. Data on postprocedural medication use and time to discharge will be obtained from routine documentation in hospital medical records systems. Data on participant satisfaction and days until return to work will be obtained at the 2-week follow-up phone call. Complication data will be collected via medical records and follow-up phone calls. Data will not be collected from participants beyond 2 weeks postprocedure.

Baseline data will be collected to characterise the study groups and to examine whether the groups are balanced with respect to important variables. These data will comprise basic demographic information (age, sex, body mass index), use of regular oral and topical analgesia, medications administered during the procedure, duration of procedure and the proceduralist, who will be will be recorded in a deidentified manner using a coding system only known to data collectors. This latter data point is to identify how many different proceduralists were involved in the study, and whether different proceduralists were balanced across study groups. These data are critical to address confounding as in clinical practice, it is thought that variation in postprocedural pain may be partly attributed to variation in proceduralist technique. Proceduralists’ identities will not be disclosed under any circumstances and will only be known to those extracting the primary data. No proceduralist-level outcome data analyses will be performed.

Additional data for subgroup analyses will comprise number of haemorrhoids banded; highest grade of haemorrhoid banded; history of previous haemorrhoid-related...
procedures and presence of anal pain as a preprocedural symptom. These data will be obtained from the operation report, medical records and the postprocedural follow-up phone calls.

For the health systems cost analysis, we will collect the item costs of the LA agent for submucosal infiltration and PNB; equipment for LA injection; labour (time) of injecting LA; postprocedural medications; and time spent in recovery.

A graphical summary of study activities is shown in figure 1.

**Figure 1** Study design.

### Data management and confidentiality

All data will be collected and stored using Research Electronic Data Capture. Data collected in the trial will be linked to participants’ hospital identifier numbers only. No identifying information will be recorded from medical records. Hospital identifier numbers are only reidentifiable to staff members of participating health services, who are bound by the relevant confidentiality agreements for use of medical records systems. Individuals will be asked to consent to the use of their information for this project only; data will not be used for unspecified future research projects.

### Statistical methods

Statistical analyses will be performed using GraphPad Prism V.9.0 (GraphPad Software, San Diego, California, USA) and StataBE V.17.0 (StataCorp). Categorical data will be expressed as frequency (percentage). Univariate and multivariate categorical variables will be compared using the $\chi^2$ test and logistic regression, respectively. Continuous variables will be expressed as mean (SD) and median (IQR) depending on the normality. Normality will be assessed using the D’Agostino-Pearson test. As there are three groups, parametric and non-parametric continuous variables will be compared using the one-way analysis of variance test and Kruskal-Wallis test, respectively. Participants in each group will be compared over time using the paired Student’s t-test for parametric data and the Wilcoxon signed rank test for non-parametric data. $P$ values <0.05 are considered statistically significant. All participants will be analysed per intention-to-treat principles.
METHODS: DATA MONITORING AND HARMs

Given that this study is not trialling any new therapeutic goods or procedures, not subject to commercial sponsorship or competing interests, and involves interventions associated with a low risk of harm, a formal data monitoring committee will not be established. However, a senior member of the research team will be specifically tasked with adverse event monitoring and handling. Study investigator details will be made available to participants and perioperative nursing staff to enable the reporting of events. Participant medical records will also be regularly checked for any adverse events documented in the periprocedural period.

Interim analyses of the results will be performed at 50% recruitment, by an independent investigator not involved in other study activities. If a statistically significant difference is found between postprocedural opioid use and postprocedural pain scores at this time, recruitment will be ceased.

Patient and public involvement statement

Patients or members of the public were not involved in the design, conduct, reporting or dissemination plans of this research.

ETHICS AND DISSEMINATION

Research ethics approval

This study has received Human Research Ethics Approval from the Austin Health Human Research Ethics Committee (March 2022). A minor amendment to the recruitment strategy and additional secondary outcome measures were then approved by this Ethics Committee in June 2022, at less than 10% recruitment. This amendment has since been communicated to all investigators and the trial registry.

Consent

Individual, fully informed written consent will be obtained from all participants. Investigators will inform participants of the study in the week prior to their RBL procedure via a phone call, and then obtain signed consent from all participants on the day of their procedure. The preliminary phone call ensures that there is adequate time for researchers to explain the study and for patients to consider their participation. At this time, researchers will also ask patients if they would like to be sent the participant information and consent form (PICF) (online supplemental appendix 1).

As this is a double-blinded study, to be included, participants must consent to undergoing all three of the possible study interventions (LA, PNB, no local or regional analgesia), with the knowledge that they will receive one of the possible interventions. The risks and benefits of each of these interventions will be explained in reasonable detail to enable each participant to make an informed decision. To reduce the risk of coercion, those recruiting participants will be reminded to explicitly state that the decision to participate in the study will have no effect on patients’ procedure timing, relationship with caregivers or standard of care.

In addition to providing consent to undergo the study interventions, to be included in the study, participants must consent to the collection of their health information via their hospital medical records, which will be accessed using their hospital identifier number. They must also consent to follow-up phone call(s) in the postprocedural period for data collection.

Handling of withdrawals and replacement

Participants may withdraw from the study at any point up until their procedure, and following their procedure, until the study closing date (documented on the PICF). Participants may withdraw without providing a reason. If participants choose to provide a reason, this will be documented in the interest of adverse event monitoring. Following participant withdrawal, researchers will not collect any further data from that participant, however, data already collected will be retained for the purposes of data analyses and monitoring. This has been stated in the PICF and if patients do not wish to have their data handled in this way, they are advised to inform researchers of this before participating in the study.

If participants withdraw from this study within the recruitment period, further participants will be recruited as replacement. The target sample size for this study is an inflation of the calculated sample size to ensure redundancy.

Access to data

The final trial dataset will be accessible by study investigators only. To reduce the risk of identifying individual participants, linked individual-level data will not be made available. Aggregate raw data can be provided on request to the corresponding author.

Dissemination policy

Trial results will be published in a peer-reviewed journal, and presented at academic conferences and departmental meetings of the involved sites. A lay summary of the trial results will also be made available to study participants, on request to the corresponding author. Authorship eligibility will be determined as per the International Committee of Medical Journal Editors guidelines.

Twitter Eleanor G R Watson @dreleanorwatson and Kirby R Qin @DrKirbyQin

Contributors EGR Watson designed the study and was the primary author of the manuscript. DMP conceived the study and assisted in study design. KRQ authored the statistical analyses section of the protocol. PS, AB, HMM and DMP were responsible for the overall supervision of the project. All authors contributed to revising and editing the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.
Provenance and peer review  Not commissioned; externally peer reviewed.

Supplemental material  This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access  This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD  Eleanor G R Watson http://orcid.org/0000-0003-3614-5132

REFERENCES