ORIGINAL CONTRIBUTION

# A Randomized Controlled Trial of Topical Analgesia Posthemorrhoidectomy (TAPH Trial)

James Z. Jin, M.B.Ch.B., Ph.D.[1] • Weisi Xia, M.B.Ch.B., Ph.D.[1] • Runzhe Gao, B.Sc., M.Sc.[2]
Alain C. Vandal, Ph.D.[2] • Maree Weston, M.B.Ch.B., F.R.A.C.S.[3]
Lincoln Israel, M.B.Ch.B., F.R.A.C.S.[3] • Andrew Connolly, M.B.Ch.B., F.R.A.C.S.[3]
Primal (Parry) Singh, M.B.Ch.B., Ph.D., F.R.A.C.S.[1,3] • Darren Svirskis, B.H.B., B.Pharm., Ph.D.[1,4]
Andrew Hill, M.B.Ch.B., M.D., F.R.A.C.S.[1,3]

1 Department of Surgery, South Auckland Clinical School, The University of Auckland, Auckland, New Zealand
2 Department of Statistics, The University of Auckland, Auckland, New Zealand
3 Department of Surgery, Te Whatu Ora Health New Zealand Counties Manukau, Auckland, New Zealand
4 School of Pharmacy, The University of Auckland, Auckland, New Zealand.

***BACKGROUND:*** Postoperative pain remains the greatest problem after hemorrhoidectomy. Pain is hypothesized to arise from bacterial infection, sphincter spasm, and local inflammation.

***OBJECTIVE:*** This trial was conducted to assess the effects of metronidazole, diltiazem, and lidocaine on posthemorrhoidectomy pain.

***DESIGN:*** A double-blinded randomized controlled factorial trial.

***SETTINGS:*** This multicenter trial was conducted in Auckland, New Zealand.

***PATIENTS:*** A total of 192 participants were randomly assigned (1:1:1:1) into 4 parallel arms.

***INTERVENTIONS:*** Participants were randomly assigned into 1 of 4 groups receiving topical treatment with 10% metronidazole, 10% metronidazole + 2% diltiazem, 10% metronidazole + 4% lidocaine, or 10% metronidazole + 2% diltiazem + 4% lidocaine. Participants were instructed to apply treatment to the anal verge 3 times daily for 7 days.

***MAIN OUTCOME MEASURES:*** The primary outcome was pain on the visual analog scale on day 4. The secondary outcomes included analgesia usage, pain during bowel movement, and functional recovery index.

***RESULTS:*** There was no significant difference in the pain and recovery scores when diltiazem or lidocaine was added to metronidazole (score difference between presence and absence of diltiazem in the formulation: −3.69; 95% CI, −13.3 to 5.94; $p = 0.46$; between presence and absence of lidocaine: −5.67; 95% CI, −15.5 to 3.80; $p = 0.24$). The combination of metronidazole + diltiazem + lidocaine did not further reduce pain. Secondary analysis revealed a significant difference between the best (metronidazole + lidocaine) and worst (metronidazole + diltiazem + lidocaine) groups in both pain and functional recovery scores. There were no significant differences in analgesic usage, complications, or return to work between the groups. No clinically important adverse events were reported. The adverse event rate did not change in the intervention groups.

***LIMITATIONS:*** Topical metronidazole was used in the control group rather than a pure placebo.

***CONCLUSIONS:*** There was no significant difference in pain when topical diltiazem, lidocaine, or both were added to topical metronidazole. See **Video Abstract**.

***CLINICALTRIALS.GOV IDENTIFIER:*** NCT04276298.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML and PDF versions of this article on the journal's website (www.dcrjournal.com).

**Funding/Support**: Health Research Council of New Zealand (22/056) and Maurice and Phyllis Paykel Trust Project Grant 2020 (grant 203145).

**Financial Disclosure:** None reported.

Presented at the Royal Australasian College of Surgeons Annual Scientific Congress, SA, Australia, May 1 to 5, 2023.

**Correspondence:** James Jin, M.B.Ch.B., Ph.D., Department of Surgery, South Auckland Clinical School, University of Auckland, Middlemore Hospital, Private Bag 93311, Otahuhu 1640, New Zealand. E-mail: james.jin@auckland.ac.nz

Dis Colon Rectum 2024; 67: 1158–1168
DOI: 10.1097/DCR.0000000000003419

## ENSAYO CONTROLADO ALEATORIZADO DE ANALGESIA TÓPICA POSTERIOR A HEMORROIDECTOMÍA (ENSAYO TAPH)

**ANTECEDENTES:** El dolor postoperatorio sigue siendo el mayor problema tras hemorroidectomía. La hipótesis es que el dolor se debe a infección bacteriana, el espasmo esfínteriano e inflamación local.

**OBJETIVO:** Se realizó un ensayo factorial aleatorizado y controlado para evaluar los efectos del metronidazol, el diltiazem y la lidocaína en el dolor posthemorroidectomía.

**DISEÑO:** Ensayo factorial controlado aleatorizado doble ciego.

**ESCENARIO:** Se realizó un ensayo multicéntrico en Auckland, Nueva Zelanda.

**PACIENTES:** Se aleatorizó a 192 participantes (1:1:1:1) en cuatro brazos paralelos.

**INTERVENCIONES:** Los participantes se asignaron aleatoriamente a uno de los cuatro grupos que recibieron tratamiento tópico con metronidazol al 10% (M), metronidazol al 10% + diltiazem al 2% (MD), metronidazol al 10% + lidocaína al 4% (ML), o metronidazol al 10% + diltiazem al 2% + lidocaína al 4% (MDL). Se indicó a los participantes que lo aplicaran en el margen anal 3 veces al día durante 7 días.

**PRINCIPALES MEDIDAS DE RESULTADO:** El resultado primario fue el dolor en la escala analógica visual en el día 4. Los resultados secundarios incluyeron el uso de analgesia, el dolor al defecar y el índice de recuperación funcional.

**RESULTADOS:** No hubo diferencias significativas en las puntuaciones de dolor y recuperación cuando se añadió diltiazem o lidocaína al metronidazol (diferencia de puntuación entre la presencia y la ausencia de D en la formulación: -3.69; IC del 95%: -13.3; 5.94; $p$ = 0.46; entre la presencia y la ausencia de L: -5.67; IC del 95%: -15.5; 3.80; $p$ = 0.24). La combinación de MDL no redujo más el dolor. El análisis secundario reveló una diferencia significativa entre los grupos mejor (ML) y peor (MDL) tanto en las puntuaciones de dolor como en las de recuperación funcional. No hubo diferencias significativas en el uso de analgésicos, las complicaciones o la reincorporación al trabajo entre los grupos. No se notificaron eventos adversos clínicamente importantes. La tasa de eventosadversos no cambió en los grupos de intervención.

**LIMITACIONES:** Se utilizó metronidazol tópico en el grupo de control, en lugar de un placebo puro.

**CONCLUSIONES:** No hubo diferencias significativas en el dolor cuando se añadió diltiazem tópico o lidocaína, o ambos, al metronidazol tópico. (*Traducción—Dr. Jorge Silva Velazco)*



**IDENTIFICADOR DE REGISTRO DEL ENSAYO CLÍNICO:** NCT04276298

**KEY WORDS:** Analgesia; Hemorrhoidectomy; Hemorrhoids; Multimodal analgesia; Postoperative pain; Postoperative recovery; Topical analgesia.


Hemorrhoids are common and can significantly affect quality of life.[1] The most effective treatment for prolapsing and external hemorrhoids is excisional hemorrhoidectomy, which is often complicated by significant postoperative pain.[2] Postoperative pain remains the single greatest problem with this operation. The underlying problem is that the tissue must be excised to remove the prominent hemorrhoid cushions, leaving a wound at the anal verge that is well innervated by sensory fibers, which undergo trauma and stretch from defecation.[3] Significant efforts have been made over the years in the attempt to introduce new analgesic regimens and surgical techniques to reduce pain postoperatively, all with limited results.[3,4]

Mechanisms of posthemorrhoidectomy pain have been hypothesized. These include bacterial infection, sphincter spasm, and local inflammation.[5–7] Topical treatments may be an effective mechanism to target pain; they may deliver drugs directly to target tissues at high concentrations and without systemic side effects. Currently, topical treatments are not routinely used after hemorrhoidectomy, presumably because of the lack of evidence or commercially available formulations. The current standard of care for postoperative management of pain involves simple analgesia, anti-inflammatory medication, and weak opiate, along with stool softeners and sitz baths.[8] However, recent meta-analyses have demonstrated the effectiveness of topical agents on posthemorrhoidectomy pain.[5,7] Additionally, a recent randomized controlled trial (RCT) found no significant difference in pain scores between oral and topical metronidazole (M) given after hemorrhoidectomy, and most participants favored topical treatments over oral medications.[9] The use of topical analgesics as an adjunct could, therefore, be a more effective and patient-preferred means of postoperative pain relief.

Topical treatments could directly target the mechanisms of posthemorrhoidectomy pain. Both oral and topical M have been demonstrated to be equally effective against postoperative pain, presumably by reducing infection and inflammation.[6,9] Based on the literature and our center's experience, the use of oral or topical M after hemorrhoidectomy has become our standard of care.[9] Topical diltiazem (D) is a calcium channel blocker that induces smooth muscle relaxation and has previously been demonstrated to be effective for reducing sphincter spasms and pain after hemorrhoidectomy.[5] Lidocaine (L) is an effective local anesthetic and has anti-inflammatory properties.[10] Based on these 3 mechanisms, we developed a cream containing topical 10% metronidazole, 2% diltiazem, and 4%

lidocaine.[4] We anticipated that each medication would exert an effect on different mechanisms of pain. We aimed to assess whether adding D or L to M alone reduces pain and whether all 3 topical medications combined have a more significant effect on reducing pain.

## MATERIALS AND METHODS

### Study Design and Participants

The Topical Analgesia Posthemorrhoidectomy Trial was a double-blinded, multicenter, parallel-group, pragmatic, randomized controlled factorial trial conducted in 1 public and 1 private hospital in Auckland, New Zealand. Participants older than 16 years scheduled for elective hemorrhoidectomy who provided written informed consent were eligible to participate. Those excluded from the trial included patients with anal fissures discovered intraoperatively or who had any allergies or medication contraindications to any of the components of the topical treatments. Patients were excluded from the trial if they had a history of chronic pain or opioid dependence and if they had language barriers or could not provide consent.

This study was approved by the New Zealand Health and Disability Ethics Committee in June 2020 (reference No. 2020/NTB/111). The trial medication was approved by the Standing Committee on Therapeutic Trials (reference code: 20/SCOTT/81). This trial was prospectively registered with ClinicalTrials.gov (trial identifier NCT04276298). There was no change to trial protocol following commencement.

### Randomization, Masking, and Concealment

Participants were randomly assigned (1:1:1:1) to receive 1 of 4 topical treatments. Randomization was conducted in a 1:1:1:1 ratio using a computer-generated permuted block randomization sequence with a block size of 12. A single randomization schedule was implemented across the 2 centers as opposed to stratified randomization by center. This decision was made to promote concealment and balance across arms at the possible cost of balance within the centers. The randomization sequence was generated by a research assistant, independent of the study, and processed by an independent pharmacy to produce the trial medication. The concealed interventions were supplied by a Good Manufacturing Practice–certified compounding pharmacy (CompoundLabs, Wairau Valley, Auckland, New Zealand) and provided to the research fellow who was blinded to the intervention.

The participants, investigators, and biostatisticians involved in the analyses were blinded to the intervention.

### Procedures

A surgical research fellow (J.J.) recruited participants on the day of the surgery and implemented the randomization schedule. Participants underwent hemorrhoidectomy performed by 1 of 5 experienced colorectal surgeons. All excisional hemorrhoidectomy techniques were included, including open, closed, and hemorrhoidectomy with a vessel-sealing or energy device. The EuroQol 5-dimension 5-level English, Hemorrhoidal Severity Score, Short Health Scale for Hemorrhoidal Disease, Hemorrhoid Fissure Quality-of-Life Score, Quality of Recovery-15 (QoR-15) Score, and Functional Recovery Index (FRI) were collected before randomization.[11–14] Other data collected at baseline included patient demographic details, such as comorbidities, grade of hemorrhoids, medications, and BMI. The operative details were recorded.

### Interventions, Dosage, and Administration

Participants were randomized into 4 groups: group A received metronidazole 10% cream (M), group B received a combination cream containing metronidazole 10% + diltiazem 2% cream (MD), group C received a combination cream containing metronidazole 10% + lidocaine 4% (ML), and group D received a combination cream containing metronidazole 10% + diltiazem 2% + lidocaine 4% (MDL). All participants were advised to apply 2 metered dose actuations of the cream, approximately 1 mL = 0.7 g of cream, directly over the wound and inside the anal verge, 3× per day. This regimen was intended to start on the first postoperative evening and continued for 7 days afterward. A pure placebo group was not included in this study, as the efficacy of topical M has previously been demonstrated to be superior to that of placebo.[9]

### Surgery and Perioperative Protocol

Written informed consent was obtained on the day of surgery, before randomization. Day-case surgery was performed with the goal of discharge. Participants who were operated on late in the day or had any postoperative complications or significant comorbidities stayed overnight as inpatients but were discharged the following morning.

Participating surgeons at each center conducted hemorrhoidectomy according to their usual approach. The participants underwent general or spinal anesthesia in the lithotomy or prone position. Hemorrhoidectomy was performed according to the surgeon's preference with diathermy or vessel-sealing devices. All participants received 20 mL of 0.75% bupivacaine with adrenaline as a combined bilateral pudendal nerve block and wound infiltration. An internal anal dressing (Spongostan; Agnthos AB, Lidingö, Sweden, or KALTOSTAT alginate dressing; ConvaTec Group, Deeside, United Kingdom) was placed at the end of the operation.

Postoperative care followed a standard regimen of evidence-based multimodal analgesia according to the procedure-specific postoperative pain management

(PROSPECT) guidelines.[8] Participants received regular paracetamol, 1 g every 6 hours, and ibuprofen, 400 mg every 8 hours, with advice to take regular laxatives and undertake sitz baths twice daily. The participants were prescribed oral tramadol (50–100 mg) as required for breakthrough pain, or if intolerant, a substitute narcotic was prescribed. The participants were instructed not to use other types of topical analgesia during the study.

### Outcomes

Patients were instructed to record pain scores, recovery scores, and analgesia in a hardcopy participant diary collected 14 days postoperatively. Pain scores were recorded on a visual analog scale (VAS) consisting of a continuous 100-mm line without tick marks. Analgesic medication was recorded, and opiate-based analgesia was subsequently converted to morphine-equivalent amounts.

Participants were followed up for 14 days; this consisted of a follow-up phone call on postoperative day 2, followed by a home visit conducted on day 14 to collect the trial questionnaire completed by the participant. The cream container was inspected on day 14, and compliance was determined by visual inspection of the remaining cream. At 30 days, any further hospital visits, general practitioner visits, or prescriptions were recorded.

Data on early postoperative complications during the 2 weeks were collected. Further planned medical and surgical treatment for complications associated with treatment were recorded for up to 90 days.

***Primary outcome.*** The primary outcome was pain on the VAS, measured on day 4, the most painful postoperative day.[9]

***Secondary outcomes.*** Secondary outcomes included pain at rest and pain during bowel movement measured on the VAS across 10 postoperative time points, from days to 0 to 7, day 10, and day 14. The secondary outcomes were calculated as the time-averaged pain score and the area under the curve (AUC).

The amount of analgesia consumed was another secondary outcome, with multiple time points measured.

The FRI was measured at baseline and on postoperative days 1, 3, 5, 7, and 14, and the QoR-15 Scale was measured on postoperative days 7 and 14.

### Statistical Analysis

***Primary and secondary hypotheses.*** The primary hypothesis was that the addition of D or L would reduce pain on the VAS compared to M alone. The secondary hypothesis was that MDL would reduce pain compared to MD or ML.

***Sample size calculation.*** The sample size calculation was based on factorial design. Forty-eight participants per group were required to provide 90% power to detect a moderate difference, corresponding to a Cohen's effect of 0.6, with a difference of 16 mm on a 100-mm VAS, with a significance level of 5% (2-sided $\alpha$). This calculation allowed for an attrition rate of 10% after randomization, based on a recent RCT from our group assessing oral and topical M in postoperative pain after hemorrhoidectomy, with 53 participants in each arm and a mean VAS of 61 mm with an SD of 23 mm on day 4.[9]

***Handling of missing data.*** Under an assumption of missingness at random, missing data were multiply imputed for all baseline covariates and pre- and postrandomization outcomes using the mice package in R.[15] Fifteen copies of complete data were produced. Common baseline predictors used for multiple imputation were demographic data such as age, BMI, sex, and comorbidities. Postsurgery measurements were imputed on the basis of measurements from the same day and from similar measurements from the previous 2 days.

***Primary and secondary analyses.*** The study analyses followed a comprehensive, prespecified statistical analysis plan. The main statistical analyses were based on an intention-to-treat framework, analyzing all participants as randomized, irrespective of follow-up or subsequent treatment compliance.

Continuous outcomes, including the primary outcome, were analyzed using linear mixed-effects models, with the outcome at each time point set as repeated measures and the L and D indicators as binary factors in interaction with time (day), itself modeled as a natural cubic spline with knots at 3, 5, and 7 days. All effect estimates and confidence intervals on each day were obtained from these models. The *lme4* package was used in R for this purpose.[16] The analyses were performed over each of the multiple imputed copies of the data and pooled using Rubin's rules.[17] Further details are available in the statistical analysis plan, which were supplied with the supplemental material.

The analysis compared the 4 postoperative arms using the factorial and interaction models. In the factorial model, each compound added to M (D or L) was assumed to have a unique additive effect on the outcome, regardless of the presence or absence of another compound. A factorial model was used for the primary analysis. The interaction model was fitted as a secondary analysis, where the interaction model assumed that each formulation (M, MD, ML, and MDL) had a unique effect on the outcome. The results from the interaction model are presented alongside those from the factorial model with a $p$ value for the interaction term representing the departure from additivity of the effects of L and D when both D and L were combined with M.

Secondary analyses compared the differences in time-averaged comparisons using AUC of the 4 study arms as independent groups.

***Blind review.*** A blind review of the data was performed to reduce the estimated residual variance and to compensate for chance imbalance. Preselected covariates were selected for regression analysis, and the outcome was adjusted if partial $R^2$ values were >0.05.

### Statistical Framework

Continuous variables are summarized as means and SDs, whereas discrete variables are reported as absolute numbers and percentages in each category. All inferences were made at a 5% significance level against 2-sided alternatives. Point estimates with 95% CIs were provided for each outcome.

Linear regression was the main inferential model, with the auxiliary covariates and indicators for the presence of D and L in the formulation set as the fixed effects in factorial models, with an added interaction term between D and L in interaction models. Logistic and relative risk regressions were applied, when appropriate, for binomial outcomes. Linear mixed models were fitted to estimate fixed effects for continuous variables, with participant ID as the random intercept, effectively modeling covariance with an intraclass correlation structure. Natural cubic splines with 3 degrees of freedom were used to model the effect of the allocation group over time. Analyses were performed on 15 multiply imputed copies of the data and pooled using Rubin's method.[17]

Marginal estimates were presented graphically for each arm in the interaction model. These corresponded to the estimated expected outcomes at each assessment time point using covariate values averaged over all trial participants.

Between- and within-participant variance estimates were obtained from linear mixed effects on the original data (nonimputed).

### Sensitivity Analysis

Sensitivity analyses were performed to assess the robustness of the missingness at random assumption and the effect of participants with missing outcome data postintervention. Sensitivity analyses covered the primary and secondary outcomes and consisted of adjusted complete case analyses, unadjusted analyses of multiply imputed data, and adjusted best- and worst-case analyses of multiply imputed data.

## RESULTS

Between September 19, 2020, and January 6, 2022, 235 patients were screened for eligibility. Of these, 192 met the inclusion criteria and were randomly assigned to receive either 10% metronidazole cream (M), 10% metronidazole and 2% diltiazem cream (MD), 10% metronidazole and 4% lidocaine cream (ML), or 10% metronidazole, 2% diltiazem and 4% lidocaine cream (MDL). In total, 192 participants were included in the analysis. The Consolidated Standards of Reporting Trials diagram is shown in Figure 1. The trial was concluded when the target sample size was reached. The total attrition rate was 5.8% (n = 11). The reasons for dropout were loss to follow-up (n = 9) and withdrawal from the study (n = 2).

The baseline characteristics of the 4 groups are shown in Table 1. The results of multiple imputation are shown in Figure 2. None of the baseline characteristics considered as potential adjustments for the regression models had any missing values. The AUC results for all comparisons are presented in Supplemental Table 1 at http://links.lww.com/DCR/C350.

### Pain at Rest

The addition of D or L did not improve pain compared with M alone (score difference between presence and absence of D in the formulation: −3.69; 95% CI, −13.3 to 5.94; $p = 0.46$; between presence and absence of L: −5.67; 95% CI, −15.5 to 3.80; $p = 0.24$). Furthermore, MDL did not reduce pain compared to MD or ML. There were no significant differences among the 4 groups in the primary factorial analysis (Fig. 2A; Table 2). Therefore, we could not reject the null hypothesis. The factorial results for D effect and L effect are displayed in Supplemental Figure 1 at http://links.lww.com/DCR/C350).

In the secondary analysis using the interaction model, when the 4 groups were compared independently, there was a significant difference between the best treatment group (ML) and the worst treatment group (MDL) across multiple time points; ML had significantly less pain on days 4, 5, and 6 than MDL (day 4: ML-MDL −9.88; 95% CI, −0.27 to −19.49; $p = 0.04$). The model-based means for the pain scores for both the factorial and interaction models are shown in Figure 2. The results of the factorial and interaction models for pain at rest are shown in Table 2. The factorial model displays the effect of adding D or L to a prior group. The interaction model compares each group individually.

There was a tendency toward a reduction in pain in the MD group compared to that in the MDL group (day 3: MD-MDL; 95% CI, −9.31 to −19.31 to 0.70; $p = 0.07$), but this was only apparent for days 1, 2, and 3. There were no significant differences between the M group and the other groups.

AUC analysis comparing ML and MDL showed the greatest difference of −115.78 (−243.03 to 11.46; $p = 0.07$), with ML having the lowest overall pain scores compared to all groups (see Supplemental Table 1 at http://links.lww.com/DCR/C350).

Table 3 lists the model-based means for each group and their confidence intervals. The between- and within-participant variances were estimated at $23.6^2$ and $16.2^2$, respectively, yielding an estimated intraclass correlation coefficient of 0.68. Missing data across time for the primary outcome are reported in Supplemental Table 2 at http://links.lww.com/DCR/C350.

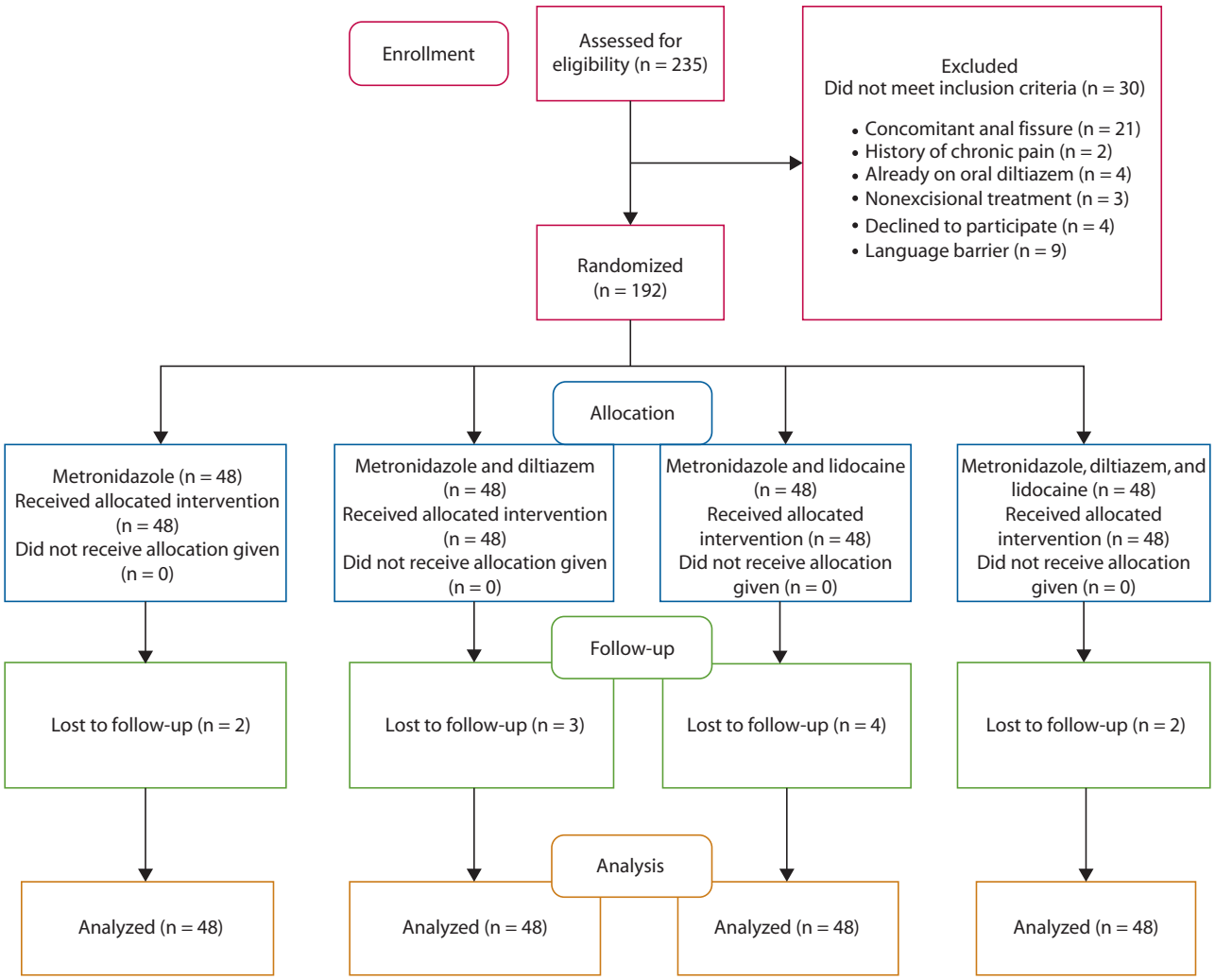


**FIGURE 1.** CONSORT diagram for participant recruitment, allocation, and analysis. CONSORT = Consolidated Standards of Reporting Trials.

### *Pain During Bowel Movement*

There were large variations in pain levels during bowel movements within the same day. There was no significant difference in pain during bowel movement on any postoperative days (Fig 3A; see Supplemental Table 3 at http://links.lww.com/DCR/C350).

### *Analgesia Usage*

There was no significant difference in the amount of milligram morphine equivalents used in factorial and interaction comparisons (Fig. 3B; see Supplemental Table 4 at http://links.lww.com/DCR/C350).

### *FRI and QoR Scores*

The ML group performed significantly better than the MDL group on multiple postoperative days, according to the interaction model. This was evident in factors 2 and 3 of the FRI.

The combined FRI scores show that the ML group was significantly better compared to the MDL group on days 5 and 7 (day 5: MDL-ML 14.56; 95% CI, 1.73–27.40; $p = 0.026$; day 7: 16.52; 95% CI, 2.64–30.41; $p = 0.02$; see Supplementary Table 5 at http://links.lww.com/DCR/C350).

The combined AUC values showed a tendency for the FRI scores in the ML group to be better than those in the MDL group (151.89; 95% CI, −160.68 to 151.52; $p = 0.056$). Domains 2 ($p = 0.021$) and 3 ($p = 0.025$) were significantly superior in ML compared to MDL.

There were no significant differences in QoR A and B scores across the 4 groups on days 7 and 14 (see Supplemental Table 6 at http://links.lww.com/DCR/C350).

### *Adverse Events and Complications*

There were no significant differences in complication rates between the 4 groups. On average, 85.4% of patients were complication-free, with 4.2% of patients requiring a further procedure for failure to heal up to 3 months postoperatively, 3.6% of patients readmitted with postoperative bleeding, and 5.8% of patients requiring admission for any other cause in the immediate 2-week postoperative period (see Supplemental Table 7 at http://links.lww.com/DCR/C350).

**TABLE 1.** Baseline characteristics by study group

| *Allocation* | *M* | *M + D* | *M + L* | *M + D + L* |
|---|---|---|---|---|
| No. of patients | 48 | 48 | 48 | 48 |
| Age, y, mean (SD) | 52.5 (14.6) | 47.6 (15.6) | 47.6 (14.1) | 46.2 (16.0) |
| Ethnicity, n (%) | | | | |
| Asian | 14 (29.2) | 15 (31.2) | 13 (27.1) | 21 (43.8) |
| European/Pakeha | 21 (43.8) | 17 (35.4) | 24 (50.0) | 14 (29.2) |
| Maori | 8 (16.7) | 9 (18.8) | 8 (16.7) | 6 (12.5) |
| Other | 3 (6.2) | 1 (2.1) | 0 (0.0) | 4 (8.3) |
| Pacifica | 2 (4.2) | 6 (12.5) | 3 (6.2) | 3 (6.2) |
| Sex, n (%) | | | | |
| Female | 33 (68.8) | 27 (56.2) | 28 (58.3) | 29 (60.4) |
| Male | 15 (31.2) | 21 (43.8) | 20 (41.7) | 19 (39.6) |
| BMI, mean (SD) | 28.4 (6.2) | 29.5 (6.3) | 28.1 (6.5) | 28.42 (6.0) |
| Diabetes status, n (%) | | | | |
| No | 45 (93.8) | 43 (89.6) | 46 (95.8) | 45 (93.8) |
| Yes | 3 (6.2) | 5 (10.4) | 2 (4.2) | 3 (6.2) |
| Operation site, n (%) | | | | |
| Public hospital | 28 (14.6) | 29 (15.1) | 35 (18.2) | 33 (17.2) |
| Private hospital | 20 (10.4) | 19 (9.9) | 13 (6.8) | 15 (7.8) |
| Position, n (%) | | | | |
| Lithotomy | 47 (24.5) | 46 (24) | 48 (25) | 48 (25) |
| Prone | 1 (0.5) | 2 (1) | 0 (0) | 0 (0) |
| Technique, n (%) | | | | |
| Diathermy | 5 (2.6) | 10 (5.2) | 5 (2.6) | 11 (5.7) |
| Ligasure/Marclamp/Voyant | 43 (22.4) | 38 (19.8) | 43 (22.4) | 37 (19.3) |
| Length of stay, n (%) | | | | |
| Day stay | 42 (21.9) | 38 (19.8) | 40 (20.8) | 44 (22.9) |
| 1 night | 5 (2.6) | 10 (5.2) | 7 (3.6) | 4 (2.1) |
| ≥2 | 1 (0.5) | 0 (0) | 1 (0.5) | 0 (0) |
| Use of suture, n (%) | | | | |
| ≥1 | 4 (2.1) | 11 (5.7) | 6 (3.1) | 9 (4.7) |
| None | 44 (22.9) | 37 (19.3) | 42 (21.9) | 39 (20.3) |
| Banding (rubber band ligation), n (%) | | | | |
| No bands | 19 (9.9) | 23 (12) | 26 (13.5) | 25 (13) |
| 1× band | 0 (0) | 2 (1) | 0 (0) | 0 (0) |
| 2× bands | 1 (0.5) | 0 (0) | 0 (0) | 1 (0.5) |
| 3× bands | 23 (12) | 18 (9.4) | 18 (9.4) | 15 (7.8) |
| 4× bands | 4 (2.1) | 5 (2.6) | 0 (0) | 0 (0) |
| Pedicles excised, n (%) | | | | |
| 1 pedicle | 2 (1) | 5 (2.6) | 2 (1) | 8 (4.2) |
| 2 pedicles | 9 (4.7) | 10 (5.2) | 11 (5.7) | 8 (4.2) |
| 3 pedicles | 37 (19.3) | 33 (17.2) | 35 (18.2) | 32 (16.7) |
| Baseline ASA, n (%) | | | | |
| ASA 1 | 24 (12.5) | 21 (10.9) | 25 (13) | 28 (14.6) |
| ASA 2 | 20 (10.4) | 19 (9.9) | 20 (10.4) | 15 (7.8) |
| ASA 3 | 4 (2.1) | 7 (3.6) | 3 (1.6) | 5 (2.6) |
| Anemia, n (%) | | | | |
| Present | 3 (1.6) | 3 (1.6) | 2 (1) | 1 (0.5) |
| None | 45 (23.4) | 45 (23.4) | 46 (24) | 47 (24.5) |

Percentages were calculated by either subgroup total (N = 48) or by study total (N = 192).D = diltiazem; L = lidocaine; M = metronidazole.

Minor adverse events reported for M, MD, ML, and MDL were 5, 6, 4, and 6 out of 48, respectively. Major adverse events were reported as 6, 5, 2, and 5 out of 48 for M, MD, ML, and MDL, respectively.

Compliance was satisfactory, with 89% of participants reporting no issues with cream use. Subjective stinging or irritation when using the cream was reported by 6% of participants overall, with significantly more participants in the D arms experiencing stinging and irritation than those in other arms ($p = 0.044$; see Supplemental Table 8 at http://links.lww.com/DCR/C350).

There was no difference in the number of patients lost to follow-up or withdrawal between the 4 groups (n = 11; 5.7%). There were no significant differences in the number of additional prescriptions over 30 days (see Supplemental Table 8 at http://links.lww.com/DCR/C350). There was no significant difference in the number of those who returned to work within 14 days; on average,

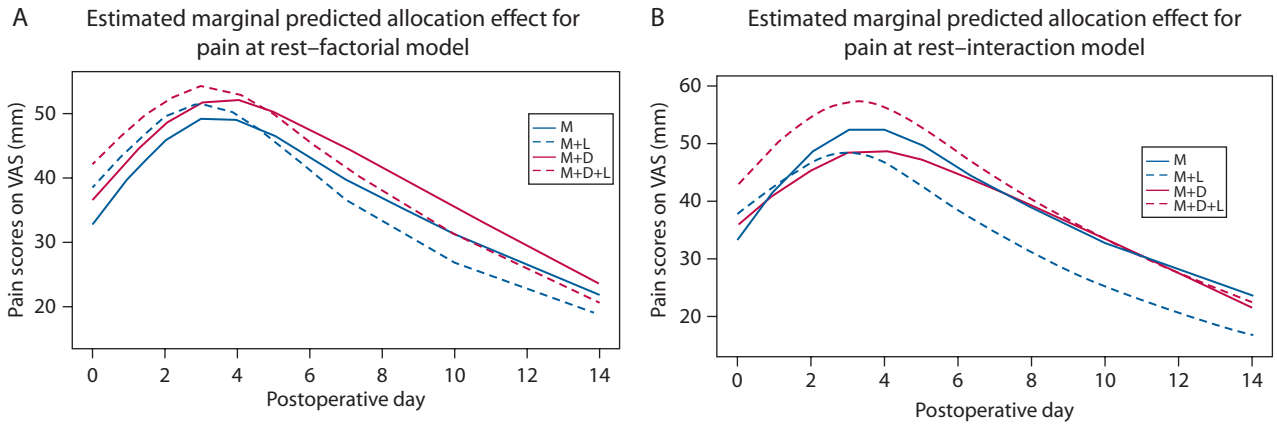


**FIGURE 2.** Estimated marginal allocation effect for pain scores at rest on the visual analog scale according to the (A) factorial model and (B) interaction model.

40% returned to work by day 14. There was no significant difference in the number of days until return to work, which averaged 9.2 days overall (see Supplemental Table 9 at http://links.lww.com/DCR/C350).

### *Sensitivity Analysis*

The primary outcome underwent sensitivity analysis. There was no divergence of CI bands when comparing extreme CI bands with CIs from the primary analysis. Extreme CI bands were plotted from the lowest lower bound and the highest upper bound chosen for all 4 types of sensitivity analyses (see Supplemental Figures 2 and 3 at http://links.lww.com/DCR/C350).

## *DISCUSSION*

To our knowledge, this is the first RCT to investigate the effects of different combinations of topical therapies on improving pain and recovery after hemorrhoidectomy. There was no significant effect observed when either D or L was added to M. The addition of both D and L did not further reduce pain. Secondary analysis found a statistically significant difference between the best (ML) and worst (MDL) groups on multiple postoperative days in both pain and functional recovery scores; however, the clinical significance of this is uncertain.

The cause of pain after hemorrhoidectomy is thought to be multifactorial. There are 3 hypothesized mechanisms: bacterial infection, sphincter spasm, and local inflammation.[4] In this study, we aimed to target all 3 of these mechanisms. The results of this study contrast with findings from the literature. Recent meta-analyses have shown that D is effective in reducing pain after hemorrhoidectomy, likely because of the reduction in sphincter spasm.[5] D has been shown to induce internal anal sphincter muscle relaxation in vitro, and RCTs have shown that it effectively reduces pain to a significant degree.[18] We were unable to observe any analgesic effect of D compared to M alone. This may be, at least partially, because of localized irritation experienced by patients using D, which may attribute to bias. We found that significantly more participants experienced a localized transient sensation of stinging in arms containing D. There was no explanation for why patients may experience irritation after using D, as we were unable to find reported interactions when D was combined with other medications.

Local anesthetics are often infiltrated to reduce pain after hemorrhoidectomy, although the effect is short lived. Bilateral pudendal nerve blocks have been established as effective methods for regional anesthesia.[19] The effectiveness of topical anesthetic creams in reducing pain after hemorrhoidectomy remains unclear. A L and prilocaine mixture has been shown to be effective (eutectic mixture of local anesthetics); however, this effect has not been demonstrated in other trials evaluating L alone.[20] We were unable to demonstrate the analgesic efficacy of L in our trial. There was no significant difference in analgesic efficacy when examining the effect of L in the factorial analysis. Although ML was found to be significantly better than MDL, the use of ML over M alone could not be justified because of the lack of difference.

The efficacy of postoperative topical analgesics in alleviating posthemorrhoidectomy pain remains undetermined. In an effort to standardize postoperative regimens that may impact pain, we have endeavored to control variables such as analgesic prescription and adjunctive measures, such as sitz baths, as best as possible. As this study is a pragmatic RCT, we are limited to drawing conclusions based on the results of the randomized arms. Overall, it is unclear why the addition of D or L did not reduce pain compared with M alone. It is possible that the analgesic effects are not additive. A possible reason for this is that the M control arm previously has analgesic and anti-inflammatory effects.[9] The addition of further topical medication may not be able to further exert a clinically meaningful effect. The efficacy of topical treatments remains unclear, as previous studies were based on relatively small sample sizes, with low-certainty evidence.[5] Further high-quality placebo-controlled studies should be

**TABLE 2.** Comparison of pain scores for all postoperative days displaying both factorial and interaction model results

| | Comparison | | Factorial fit | | | Interaction fit | | |
|---|---|---|---|---|---|---|---|---|
| Day | Arm 1 | Arm 2 | Estimates (arm 2 – arm 1) | 95% CI | p | Estimate (arm 2 – arm 1) | 95% CI | p |
| Day 0 | M | M + L | 5.6 | –2.6 to 13.9 | 0.18 | 4.3 | –7.3 to 15.9 | 0.48 |
| | | M + D | 3.8 | –4.2 to 11.8 | 0.36 | 2.3 | –8.9 to 13.5 | 0.70 |
| | | M + D + L | 9.4 | 1.4 to 17.4 | 0.10 | 9.6 | –1.6 to 20.7 | 0.09 |
| | M + L | M + D + L | 3.8 | –4.2 to 11.8 | 0.36 | 5.3 | –6.2 to 16.8 | 0.37 |
| | M + D | M + D + L | 5.6 | –2.6 to 13.9 | 0.18 | 7.2 | –4.2 to 18.7 | 0.22 |
| | | | | Interaction term: | | 3.0 | –13.2 to 19.1 | 0.73 |
| Day 1 | M | M + L | 4.7 | –2.3 to 11.7 | 0.19 | 1.2 | –8.7 to 11.0 | 0.83 |
| | | M + D | 3.1 | –3.7 to 10.0 | 0.38 | –0.6 | –10.2 to 9.1 | 0.92 |
| | | M + D + L | 7.8 | 1.0 to 14.7 | 0.11 | 8.0 | –1.6 to 17.7 | 0.10 |
| | M + L | M + D + L | 3.1 | –3.7 to 10.0 | 0.38 | 6.9 | –3.0 to 16.7 | 0.17 |
| | M + D | M + D + L | 4.7 | –2.3 to 11.7 | 0.19 | 8.6 | –1.3 to 18.4 | 0.09 |
| | | | | Interaction term: | | 7.4 | –6.4 to 21.3 | 0.30 |
| Day 2 | M | M + L | 3.7 | –3.1 to 10.5 | 0.29 | –1.7 | –11.2 to 7.8 | 0.74 |
| | | M + D | 2.7 | –4.1 to 9.5 | 0.44 | –2.9 | –12.4 to 6.7 | 0.57 |
| | | M + D + L | 6.4 | –0.4 to 13.2 | 0.19 | 6.6 | –3.0 to 16.2 | 0.18 |
| | M + L | M + D + L | 2.7 | –4.1 to 9.5 | 0.44 | 8.3 | –1.3 to 17.8 | 0.09 |
| | M + D | M + D + L | 3.7 | –3.1 to 10.5 | 0.29 | 9.4 | –0.3 to 19.1 | 0.06 |
| | | | | Interaction term: | | 11.2 | –2.3 to 24.6 | 0.10 |
| Day 3 | M | M + L | 2.5 | –4.6 to 9.5 | 0.5 | –4.1 | –13.7 to 5.6 | 0.42 |
| | | M + D | 2.7 | –4.4 to 9.6 | 0.47 | –4.0 | –13.8 to 5.80 | 0.43 |
| | | M + D + L | 5.1 | –1.9 to 12.1 | 0.32 | 5.3 | –4.6 to 15.2 | 0.30 |
| | M + L | M + D + L | 2.6 | –4.4 to 9.6 | 0.47 | 9.3 | –0.4 to 19.1 | 0.06 |
| | M + D | M + D + L | 2.5 | –4.6 to 9.5 | 0.50 | 9.3 | –0.7 to 19.3 | 0.07 |
| | | | | Interaction term: | | 13.4 | –0.4 to 27.1 | 0.06 |
| Day 4 | M | M + L | 1.0 | –5.9 to 7.9 | 0.80 | –5.7 | –15.2 to 3.9 | 0.24 |
| | | M + D | 3.1 | –3.8 to 9.9 | 0.39 | –3.7 | –13.3 to 5.9 | 0.46 |
| | | M + D + L | 4.0 | –2.8 to 10.9 | 0.42 | 4.2 | –5.5 to 13.9 | 0.40 |
| | M + L | M + D + L | 3.1 | –3.8 to 9.9 | 0.39 | 9.9 | 0.3 to 19.5 | **0.04** |
| | M + D | M + D + L | 1.0 | –5.9 to 7.9 | 0.80 | 7.9 | –1.9 to 17.7 | 0.12 |
| | | | | Interaction term: | | 13.6 | 0.0 to 27.1 | **0.05** |
| Day 5 | M | M + L | –0.6 | –7.3 to 6.0 | 0.86 | –6.7 | –15.9 to 2.5 | 0.16 |
| | | M + D | 3.8 | –2.9 to 10.5 | 0.27 | –2.4 | –11.7 to 6.9 | 0.63 |
| | | M + D + L | 3.2 | –3.5 to 9.8 | 0.52 | 3.3 | –6.07 to 12.7 | 0.50 |
| | M + L | M + D + L | 3.8 | –2.9 to 10.5 | 0.27 | 10.0 | 0.6 to 19.4 | **0.04** |
| | M + D | M + D + L | –0.6 | –7.3 to 6.0 | 0.86 | 5.7 | –3.8 to 15.3 | 0.24 |
| | | | | Interaction term: | | 12.4 | –0.8 to 25.7 | 0.07 |
| Day 6 | M | M + L | –2.1 | –8.8 to 4.7 | 0.56 | –7.3 | –16.8 to 2.1 | 0.13 |
| | | M + D | 4.5 | –2.3 to 11.2 | 0.20 | –0.9 | –10.4 to 8.6 | 0.86 |
| | | M + D + L | 2.4 | –4.4 to 9.2 | 0.64 | 2.6 | –7.0 to 12.1 | 0.61 |
| | M + L | M + D + L | 4.5 | –2.3 to 11.2 | 0.20 | 9.9 | 0.3 to 19.5 | **0.04** |
| | M + D | M + D + L | –2.1 | –8.8 to 4.7 | 0.56 | 3.5 | –6.2 to 13.2 | 0.49 |
| | | | | Interaction term: | | 10.8 | –2.7 to 24.3 | 0.12 |
| Day 7 | M | M + L | –3.1 | –10.2 to 3.9 | 0.39 | –7.7 | –17.5 to 2.1 | 0.12 |
| | | M + D | 4.9 | –2.1 to 11.9 | 0.17 | 0.2 | –9.7 to 10.0 | 0.98 |
| | | M + D + L | 1.8 | –5.3 to 8.8 | 0.74 | 1.9 | –8.0 to 11.9 | 0.72 |
| | M + L | M + D + L | 4.9 | –2.1 to 11.9 | 0.17 | 9.6 | –0.3 to 19.6 | 0.06 |
| | M + D | M + D + L | –3.1 | –10.2 to 3.9 | 0.39 | 1.8 | –8.29 to 11.8 | 0.74 |
| | | | | Interaction term: | | 9.5 | –4.6 to 23.5 | 0.19 |
| Day 10 | M | M + L | –4.2 | –11.4 to 2.9 | 0.25 | –7.8 | –17.7 to 2.2 | 0.13 |
| | | M + D | 4.5 | –2.6 to 11.5 | 0.22 | 0.8 | –9.2 to 10.8 | 0.89 |
| | | M + D + L | 0.2 | –6.8 to 7.3 | 0.97 | 0.4 | –9.6 to 10.4 | 0.94 |
| | M + L | M + D + L | 4.5 | –2.6 to 11.5 | 0.22 | 8.2 | –1.8 to 18.2 | 0.11 |
| | M + D | M + D + L | –4.2 | –11.4 to 2.9 | 0.25 | –0.4 | –10.5 to 9.8 | 0.95 |
| | | | | Interaction term: | | 7.4 | –6.8 to 21.6 | 0.31 |
| Day 14 | M | M + L | –3.0 | –11.2 to 5.3 | 0.49 | –6.5 | –18.0 to 5.0 | 0.27 |
| | | M + D | 1.8 | –6.3 to 9.8 | 0.68 | –1.9 | –13.3 to 9.4 | 0.75 |
| | | M + D + L | –1.2 | –9.3 to 6.8 | 0.84 | –1.1 | –12.4 to 10.3 | 0.87 |
| | M + L | M + D + L | 1.8 | –6.3 to 9.8 | 0.68 | 5.5 | –6.0 to 17.0 | 0.36 |
| | M + D | M + D + L | –3.0 | –11.2 to 5.3 | 0.49 | 0.9 | –10.6 to 12.4 | 0.89 |
| | | | | Interaction term: | | 7.4 | –8.8 to 23.6 | 0.38 |

The factorial models displays the effect of the addition of D or L. The interaction model compares all 4 groups separately. Boldface indicates statistical significance $p < 0.05$.
D = diltiazem; L = lidocaine; M = metronidazole.

**TABLE 3.** Model-based means and CIs for pain scores at rest

| | | Pain score at rest (factorial model) | | | Pain score at rest (interaction model) | | |
|---|---|---|---|---|---|---|---|
| *Time* | *Group* | *Estimates* | *95% CI lower* | *95% CI upper* | *Estimates* | *95% CI lower* | *95% CI upper* |
| Day 0 | M | 32.8 | 26.0 | 39.7 | 33.5 | 25.6 | 41.3 |
| | MD | 36.6 | 29.4 | 43.8 | 35.8 | 27.5 | 44.0 |
| | ML | 38.4 | 31.4 | 45.4 | 37.7 | 29.5 | 46.0 |
| | MDL | 42.2 | 35.4 | 49.0 | 43.0 | 35.1 | 50.9 |
| Day 1 | M | 39.9 | 34.0 | 45.9 | 41.7 | 34.9 | 48.5 |
| | MD | 43.1 | 37.0 | 49.2 | 41.1 | 34.1 | 48.2 |
| | ML | 44.6 | 38.7 | 50.6 | 42.9 | 35.9 | 49.8 |
| | MDL | 47.8 | 41.8 | 53.8 | 49.7 | 42.8 | 56.7 |
| Day 2 | M | 45.8 | 39.9 | 51.6 | 48.5 | 41.8 | 55.2 |
| | MD | 48.5 | 42.5 | 54.4 | 45.6 | 38.7 | 52.5 |
| | ML | 49.5 | 43.7 | 55.3 | 46.8 | 40.1 | 53.5 |
| | MDL | 52.2 | 46.2 | 58.2 | 55.1 | 48.2 | 62.0 |
| Day 3 | M | 49.1 | 43.1 | 55.1 | 52.4 | 45.5 | 59.2 |
| | MD | 51.8 | 45.6 | 57.9 | 48.3 | 41.3 | 55.4 |
| | ML | 51.6 | 45.5 | 57.7 | 48.3 | 41.4 | 55.2 |
| | MDL | 54.2 | 48.1 | 60.4 | 57.6 | 50.5 | 64.8 |
| Day 4 | M | 49.1 | 43.2 | 55.0 | 52.4 | 45.7 | 59.1 |
| | MD | 52.2 | 46.2 | 58.1 | 48.7 | 41.8 | 55.6 |
| | ML | 50.0 | 44.1 | 56.0 | 46.7 | 39.9 | 53.5 |
| | MDL | 53.1 | 47.1 | 59.2 | 56.6 | 49.6 | 63.6 |
| Day 5 | M | 46.6 | 40.9 | 52.3 | 49.6 | 43.1 | 56.2 |
| | MD | 50.4 | 44.6 | 56.2 | 47.2 | 40.5 | 53.9 |
| | ML | 46.0 | 40.2 | 51.8 | 42.9 | 36.4 | 49.5 |
| | MDL | 49.8 | 43.9 | 55.7 | 53.0 | 46.2 | 59.8 |
| Day 6 | M | 43.1 | 37.3 | 49.0 | 45.7 | 39.1 | 52.4 |
| | MD | 47.6 | 41.7 | 53.6 | 44.8 | 38.0 | 51.7 |
| | ML | 41.1 | 35.2 | 46.9 | 38.4 | 31.8 | 45.1 |
| | MDL | 45.5 | 39.6 | 51.5 | 48.3 | 41.4 | 55.3 |
| Day 7 | M | 39.7 | 33.7 | 45.8 | 42.0 | 35.1 | 49.0 |
| | MD | 44.6 | 38.4 | 50.8 | 42.2 | 35.0 | 49.3 |
| | ML | 36.6 | 30.6 | 42.6 | 34.3 | 27.4 | 41.2 |
| | MDL | 41.5 | 35.3 | 47.7 | 43.9 | 36.8 | 51.1 |
| Day 10 | M | 31.1 | 24.9 | 37.3 | 32.9 | 25.8 | 39.9 |
| | MD | 35.6 | 29.2 | 41.9 | 33.6 | 26.4 | 40.9 |
| | ML | 26.9 | 20.8 | 33.0 | 25.1 | 18.1 | 32.1 |
| | MDL | 31.3 | 25.1 | 37.6 | 33.3 | 26.1 | 40.5 |
| Day 14 | M | 21.7 | 14.8 | 28.7 | 23.5 | 15.5 | 34.4 |
| | MD | 23.5 | 16.4 | 30.5 | 21.5 | 13.4 | 29.7 |
| | ML | 18.8 | 11.7 | 25.9 | 17.0 | 8.7 | 25.2 |
| | MDL | 20.5 | 13.5 | 27.5 | 22.4 | 14.4 | 30.5 |

D = diltiazem; L = lidocaine; M = metronidazole.

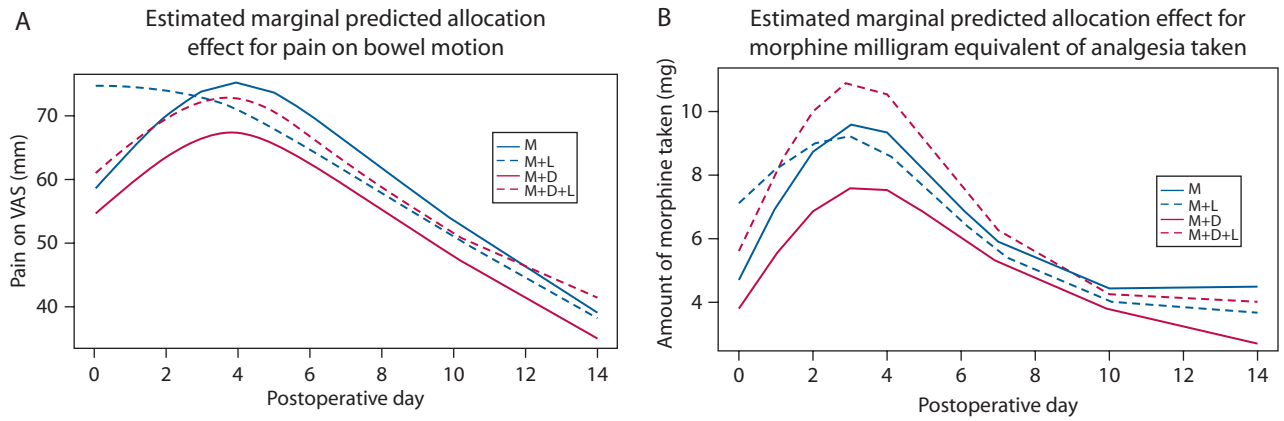


**FIGURE 3.** A, Estimated marginal allocation effect for pain scores on bowel movement on the visual analog scale according to the interaction model. B, Estimated marginal allocation effect for the amount of morphine milligram equivalent taken according to the interaction model.

conducted to examine the effects of topical agents on pain after hemorrhoidectomy.

According to a factorial model, the study was powered to detect a difference between the intervention and control groups by an average of 16 mm on the VAS. When analyzing our results using an interaction model, the comparisons were underpowered. Furthermore, head-to-head RCTs require more participants to detect a difference, where a mean difference of 10 mm on the VAS would need a sample size of 142 in each group.

The strength of this study is its factorial design, which allows for a moderately large sample size to detect a significant difference for either D or L. Other strengths include its double-blinded nature, standardization of postoperative care, and low attrition rates. A limitation that persists is the absence of a control group that exclusively uses a placebo to determine the impact of topical analgesia. Topical M is the active control in this scenario, as it has been established as a standard of care in our institution based on previous meta-analyses.[4,6,7] The trial was powered according to a factorial design as the primary analysis; therefore, limitations include the risk of a type 2 error when analyzing according to an interaction model, as each arm was inadequately powered to detect a significant difference compared to other arms independently. Any statistical significance from secondary analyses should also be interpreted with caution, as it is debatable whether this could represent a type 1 error. The trial was a pragmatic trial with participants using a cream and multimodal analgesia regimen, as instructed. However, the degree of compliance was unclear and the actual amount used at the time of application and frequency of use could not be measured.

## CONCLUSIONS

The addition of topical D or L to topical M alone did not reduce pain. The combination of MDL cream did not reduce pain. There was no convincing evidence of a significant difference between the 4 randomized groups. Secondary analysis found combination ML cream significantly improved pain and recovery scores compared to combination MDL cream. Further high-quality placebo-controlled studies with large sample sizes should evaluate the role of topical analgesics as part of a multimodal pain relief regimen to enhance recovery after day-case anorectal surgery.

## REFERENCES


1. Jin J, Xia W, Connolly A, Hill AG. Symptom-based scoring for haemorrhoidal disease: a systematic review. *Colorectal Dis*. 2020;22:1518–1527.
2. Jin JZ, Bhat S, Lee K-T, Xia W, Hill AG. Interventional treatments for prolapsing haemorrhoids: network meta-analysis. *BJS Open*. 2021;5:zrab091.
3. Sammour T. Pain after hemorrhoidectomy.*Dis Colon Rectum*. 2022;65:951–952.
4. Xia W, Sammour T, Hill A. Pursuit of the painless haemorrhoidectomy: current and future research directions. *ANZ J Surg*. 2020;90:656–657.
5. Jin J, Unasa H, Bahl P, Mauiliu-Wallis M, Svirskis D, Hill A. Can targeting sphincter spasm reduce post-haemorrhoidectomy pain? A systematic review and meta-analysis. *World J Surg*. 2023;47:520–533.
6. Xia W, Manning JPR, Barazanchi AWH, Su'a B, Hill AG. Metronidazole following excisional haemorrhoidectomy: a systematic review and meta-analysis. *ANZ J Surg*. 2018;88:408–414.
7. Xia W, Park B, Otutaha BF, et al. Topical analgesia following excisional haemorrhoidectomy: a systematic review and meta-analysis of randomised controlled trials. *Int J Colorectal Dis*. 2020;35:181–197.
8. Sammour T, Barazanchi AW, Hill AG; PROSPECT group (Collaborators). Evidence-based management of pain after excisional haemorrhoidectomy surgery: a PROSPECT review update. *World J Surg*. 2017;41:603–614.
9. Xia W, Barazanchi AWH, MacFater WS, et al. Topical versus oral metronidazole after excisional hemorrhoidectomy: a double-blind randomized controlled trial. *Dis Colon Rectum*. 2022;65:1362–1372.
10. Castro I, Carvalho P, Vale N, Monjardino T, Mourão J. Systemic anti-inflammatory effects of intravenous lidocaine in surgical patients: a systematic review and meta-analysis. *J Clin Med*. 2023;12:3772.
11. Abramowitz L, Bouchard D, Siproudhis L, et al. Psychometric properties of a questionnaire (HEMO-FISS-QoL) to evaluate the burden associated with haemorrhoidal disease and anal fissures. *Colorectal Dis*. 2019;21:48–58.
12. Rørvik HD, Styr K, Ilum L, et al. Hemorrhoidal Disease Symptom Score and Short Health ScaleHD: new tools to evaluate symptoms and health-related quality of life in hemorrhoidal disease. *Dis Colon Rectum*. 2019;62:333–342.
13. Wong J, Tong D, De Silva Y, Abrishami A, Chung F. Development of the functional recovery index for ambulatory surgery and anesthesia. *Anesthesiology*. 2009;110:596–602.
14. Kleif J, Waage J, Christensen KB, Gögenur I. Systematic review of the QoR-15 score, a patient-reported outcome measure measuring quality of recovery after surgery and anaesthesia. *Br J Anaesth*. 2018;120:28–36.
15. van Buuren S, Groothuis-Oudshoorn, K. mice: Multivariate imputation by chained equations in R. *J Stat Softw*. 2011;45:1–67.
16. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4.*J Stata Softw*. 2014;67:1–48.
17. Rubin DB. *Multiple Imputation for Survey Nonresponse*. New York: Wiley, 1987.
18. Jonas-Obichere M, Scholefield JH, Acheson A, Mundey M, Tyler H, Wilson VG. Comparison of the effects of nitric oxide donors and calcium channel blockers on the intrinsic myogenic tone of sheep isolated internal anal sphincter. *Br J Surg*. 2005;92:1263–1269.
19. Xia W, MacFater HS, MacFater WS, et al. Local anaesthesia alone versus regional or general anaesthesia in excisional haemorrhoidectomy: a systematic review and meta-analysis. *World J Surg*. 2020;44:3119–3129.
20. Shiau JM, Hung KC, Chen HH, Chen WH, Wu YH, Tseng CC. Combination of topical EMLA with local injection of lidocaine: superior pain relief after Ferguson hemorrhoidectomy. *Clin J Pain*. 2007;23:586–590.