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Original Research Article

Pre-cooling for Reducing Pain from Local Anesthetic Injections for Hemorrhoidectomy: An Open-label, Randomized, Crossover Trial

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Abstract

Objectives: Excisional hemorrhoidectomy (EH) is sometimes same-day surgery under local anesthesia (LA); however, the LA injection can be painful. We conducted an open-label, crossover, randomised controlled trial to evaluate the efficacy and safety of pre-cooling in reducing pain associated with LA injection.

Methods: Patients aged ≥ 20 years undergoing bilateral EH were randomly assigned to 1 of 2 pre-cooling sequences: a cooling-first sequence and a cooling-second sequence. In the first intervention phase, 2 minutes of pre-cooling was applied before LA injection in patients randomized to the cooling-first sequence; patients in the cooling-second sequence were asked to wait for 2 minutes (without pre-cooling) before LA injection. The pre-cooling sequences and the perianal sides targeted for injection were reversed in the second intervention phase. The primary outcome was the visual analogue scale (VAS) rating for pain from LA injection, which was obtained twice for each patient. Adverse events due to pre-cooling (e.g., skin disorders) were documented.

Results: Of 114 screened patients, 51 were randomized to the cooling-first (n = 26; analyzed: n = 26) or cooling-second sequence (n = 25; analyzed: n = 25). The 2-minute pre-cooling was completed by 48 patients (94%). VAS scores for LA injection pain decreased significantly with pre-cooling compared to without (difference estimate, −1.71; 95% confidence interval, −2.12 to −1.31; p< 0.001). No adverse events were reported.

Conclusions: Two minutes of skin pre-cooling effectively and safely reduces LA injection pain in patients undergoing EH.

Keywords

local anesthesia, ice, pain management, hemorrhoidectomy, cryotherapy

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Introduction

Excisional hemorrhoidectomy (EH) is sometimes conducted under local anesthesia (LA). Pain associated with LA is a significant burden for patients. One of the options for pain management is pre-cooling. In the settings of inguinal hernia and laceration[1-3], for which procedures are conducted under LA, randomized controlled trials have demonstrated that pre-cooling can reduce the pain associated with injections. However, the effectiveness of pre-cooling has not yet been shown in the context of hemorrhoidectomy. The purpose of this randomized study was to investigate whether pre-cooling is also effective for reducing pain in hemorrhoidectomy.

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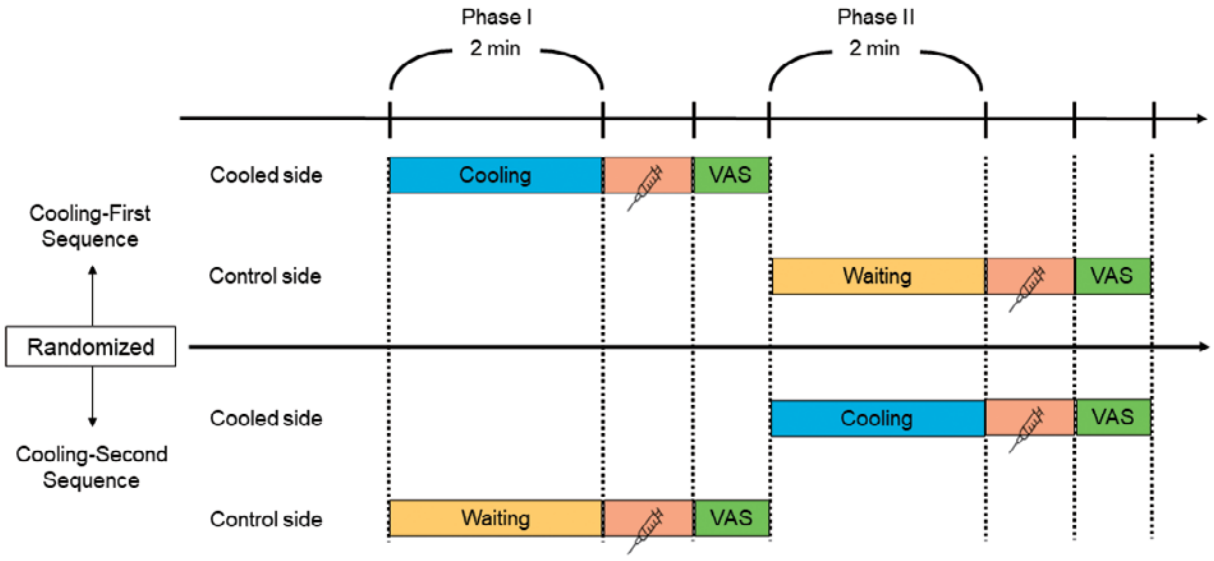

Figure 1. Schematic of the crossover study design. VAS, visual analogue scale.

Methods

The study protocol was approved by an independent ethics committee (Osaka Metropolitan University), and the trial was conducted in accordance with the Helsinki Declaration and Ethical Guidelines for Medical and Health Research Involving Human Subjects. Informed consent was obtained from each patient before their participation in the trial, and written consent was mandatory for inclusion. This trial was registered with the Japan Registry of Clinical Trials on March 23, 2022 (registration number: jRCT1051210201, https://rctportal.niph.go.jp//en).

Study design and setting

The study was designed as a single-center, open-label, crossover, randomized controlled trial (Figure 1). It was conducted at Yano Komon Geka Clinic, a small private clinic in an area with about four hundred thousand inhabitants located in the south-west region of Japan. The clinic is the only day anal surgery clinic specializing in the treatment of proctology in the area and performs over a hundred EHs per year.

In this study, it was not possible to inject anesthetic solution into both cooled and uncooled areas simultaneously. Given the inherent time difference between injecting LA in the right and left sides in a bilateral EH, a crossover study design was utilized. Moreover, to evaluate the carryover effect from phase I to phase II of the intervention, the same time interval (2 minutes) was used for both the waiting time and cooling time.

Patients were recruited from the clinic. Patients undergoing bilateral EH were assigned to 1 of 2 sequences: a cooling-first sequence and a cooling-second sequence. The treatment aspect of the study protocol began when the patient was placed in the Sims position on the operating table, and 2 intervention phases followed. In the first phase, the side (either right or left) of perianal area that had the larger hemorrhoid was pre-cooled for 2 minutes before administering LA injection for patients allocated to the cooling-first sequence. Patients allocated to the cooling-second sequence were asked to wait for 2 minutes without pre-cooling and then received LA injection on the side of the perianal area that had the larger hemorrhoid. The pre-cooling was performed with ice packs frozen at 0°C. In the second phase, the pre-cooling sequences and the sides of the perianal region that were targeted for injection were reversed for each patient. Immediately after each LA injection in both phase I and phase II, each patient was asked to use the visual analogue scale (VAS) to rate the associated pain by marking a vertical line from 0 to 10 (0, no pain; 10, the worst imaginable pain) on the VAS scale.

Participants

Patients undergoing a planned EH that was scheduled as a same-day procedure occurring between March 2022 and March 2023 were screened for participation in the study. The study enrolled patients who met all eligibility criteria, including patients: 1) with a Goligher hemorrhoid classification of grade III or IV, 2) with 1 hemorrhoid each located on the left and right sides, 3) scheduled to undergo EH during the study period, and 4) aged 20 years or older. Patients were ineligible if they: 1) had a history of anal surgery, 2) were pregnant, 3) were lactating, 4) had a lidocaine allergy, or 5) had an anal fistula or anal fissures.

Randomization

The allocation for each patient was seen by the attending surgeon when individual patient information was entered in the secured online Research Electronic Data Capture (REDCap) system[4]. The order of the pre-cooling procedure (cooling first or cooling second) was randomly assigned to patients by using permuted block randomization with a block size of 2 or 4. The random sequence used for the allocation was generated by an independent statistician.

Intervention

We used a commonly available ice pack (12 cm × 4 cm in size, 1-cm thickness) that solidifies in the freezer and froze the ice pack at 0°C. For the pre-cooling procedure, the frozen ice pack was applied for 2 minutes to a 48-cm^2 region of the perianal area including the hemorrhoid lesion. The ice pack was covered with gauze to prevent direct contact with the skin on the controlled side. Individual disposable ice packs were used for each patient. Patients were allowed to shorten the cooling time or discontinue their participation in the study at any time.

Local anesthesia

The LA used in the study was 10 mL of a 1% lidocaine solution (Xylocaine 1% injection syringe; Sandoz K.K., Tokyo, Japan; lot 26210) that had been stored at room temperature. For each cooled and controlled side in each patient, 10 mL of the solution was used, for a total of 20 mL per patient. The LA was administered around the hemorrhoid lesion by subcutaneous injection with 27-gauge needles. Injections consisted of 1 mL per puncture, with approximately 10 mL of solution administered via 10 punctures over roughly 30 seconds per side per patient.

Study outcomes

The primary outcome was the VAS score for pain experienced during LA injection. Each patient had 2 VAS scores, including ratings after the LA injections on the left and right sides. For the safety evaluation, the occurrence of adverse events related to skin pre-cooling was assessed.

Data collection

Data collection for this study was conducted using REDCap. Prior to a potentially eligible surgical procedure, a surgeon accessed REDCap to determine whether the patient met all inclusion criteria in the absence of any exclusion criteria. The patient's height, body weight, and the presence or absence of complications were then entered in REDCap. After the surgery, a surgeon entered further data in REDCap, including whether an ice pack was applied for 2 minutes or (if < 2 minutes of pre-cooling occurred) the actual time (in seconds) that an ice pack was applied, locations of each hemorrhoid, the side (left or right) of the first and second injections, 2 VAS scores recorded by the patient, and any skin impairment in the area where an ice pack was applied.

Sample size

The sample size was determined considering feasibility within the 1-year registration period. Based on prior experience at the clinic, roughly 50 patients per year who met the eligibility criteria for our study were expected to undergo EH. Thus, the target sample size was set at 50 patients. A full description of the sample size is available in Supplement file 1.

Statistical analysis

Data are presented as median (IQR) or mean (SD) values, as appropriate. For the primary analysis, a paired *t* test was performed to compare VAS scores obtained after LA injections with and without pre-cooling. The efficacy of pre-cooling was assessed on the basis of a 2-sided alpha level of $P < 0.05$. To confirm the results from another type of analysis, a linear mixed-effects model with random intercepts for individual effects and adjustments for sex, age, and phase (phase I or II) was performed. Prespecified subgroup analyses by sex and age (stratified by median value) were also performed using linear mixed-effects models. To quantify the carryover effect of pre-cooling in the first phase, the sums of the VAS scores for both intervention phases in each patient were compared between the 2 sequence groups (cooling-first vs cooling-second) using an independent *t* test. All estimates were presented with 95% confidence intervals (CI). All statistical calculations were performed using R Statistical Software (v4.2.2; R Core Team 2022).

Results

Patients flow and operative results

A total of 114 patients were screened for eligibility, and 51 patients were enrolled in the study between March 2022 and March 2023. Of these, 26 patients were allocated to the cooling-first sequence, and 25 patients were allocated to the cooling-second sequence; all patients completed the first and second VAS assessments and were included in the analysis (Figure 2). Patient characteristics are summarized in Table 1. All patients had grade III hemorrhoids. The characteristics of hemorrhoids are also summarized (Supplement file 2). The positions and sizes of hemorrhoids were well balanced between the cooled and control sides. Cooling for 2 minutes could not be completed in 3 patients (1 patient in the cooling-first sequence and 2 patients in the cooling-second sequence); the cooling times for these patients were 60 s, 90 s, and 60 s, respectively. Neither serious nor minor adverse events, such as skin problems, occurred with the 2-minute pre-cooling procedure. Operative results and complications are summarized in Table 2.

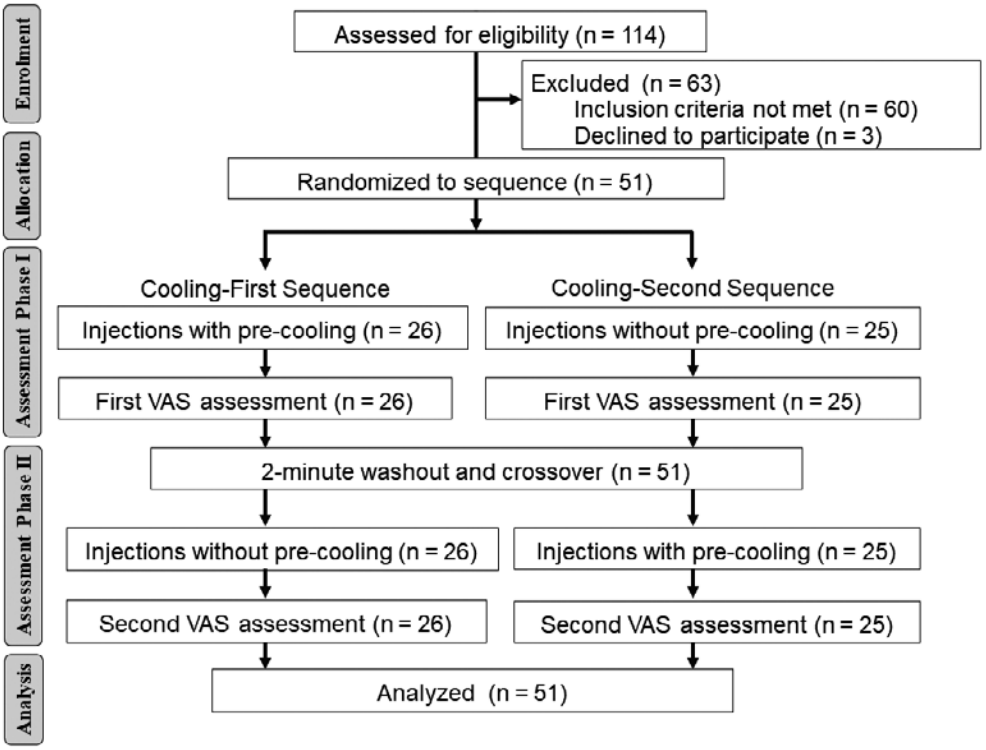

Figure 2. Patient flowchart.

Table 1. Participant Characteristics.

Demographics	Cooling-first sequence (n = 26)	Cooling-second sequence (n = 25)
Age (years) *	39 (33-47)	43 (35-47)
Sex ratio (M:F)	10:16	8:17
Height (cm) *	162 (158-169)	160 (158-164)
Weight (kg) *	59 (52-70)	54 (51-63)
BMI (kg/m2) *	22 (20-24)	21 (20-24)
Grade of hemorrhoid		
III	26 (100%)	25 (100%)
IV	0 (0%)	0 (0%)
Hemorrhoid size differential		
Right side larger	18 (69%)	18 (72%)
Left side larger	8 (31%)	7 (28%)
Comorbidity		
Hypertension	1 (4%)	1 (4%)

* Values are median (IQR). BMI, body mass index

VAS scores for pain

The VAS scores obtained during both study phases are described in Figure 3, 4, and Supplement file 3. The mean (SD) value of the overall VAS score was 5.96 (1.75), and the mean values of VAS scores obtained after LA injections with or without pre-cooling were 5.10 (1.59) and 6.81 (1.47), respectively. The paired *t* test showed a significant reduction in VAS scores after LA injection with pre-cooling compared to that without pre-cooling (difference estimate, −1.71; 95% CI, −2.12 to −1.31; $p < 0.001$). Similar results were obtained in the linear mixed-effects model analysis (Table 3). The size of the carryover effect was estimated to be rather small compared to the effect of pre-cooling (difference estimate, −0.3; 95% CI, −1.8 to 1.3; $p = 0.721$) (Supplement file 4).

Among the subgroups by sex or age, the estimated pre-cooling effects were roughly consistent with the main results; no heterogeneity in treatment effect was detected (Figure 5). Additionally, the VAS scores in a small subgroup of patients who did not complete 2 minutes of pre-cooling (n = 3) were described post hoc as having a mean difference (cooled minus control) of −2.84 (SD, 0.73) (Supplement file 5).

Discussion

In this crossover trial, we demonstrated that pre-cooling can reduce pain associated with LA injections for hemorrhoidectomy. Day surgery has become popular in recent years, and LA plays an important role in those procedures. The current findings are of value in such clinical settings. The effectiveness of pre-cooling appears to be rated by patients as a "slightly better" rather than a "much better" pain experience, as the reduction in VAS scores that was associated with pre-cooling did not exceed 2 points[5]. However,

Table 2. Operative Results and Complications.

Demographics	Cooling-first sequence (n = 26)	Cooling-second sequence (n = 25)
The number of resected hemorrhoids		
2	24 (92%)	23 (92%)
3	2 (8%)	2 (8%)
Duration of operation (min) *	13 (10-16)	12 (9-16)
Intraoperative blood loss (ml) *	12 (9-15)	14 (10-17)
The use of additional local infiltration anesthetics during the operation		
yes	3 (12%)	2 (8%)
no	23 (88%)	23 (92%)
The period from completion surgery to return home (min) *	68 (63-72)	70 (62-77)
Pain score in the next day of the operation (VAS) *	5.6 (3.6-7.9)	5.9 (4.0-8.1)
Complications		
Urinary retention	2 (8%)	1 (4%)
Fecal impaction	2 (8%)	2 (8%)
Postoperative bleeding	0 (0%)	0 (0%)
Anal stenosis	1 (4%)	1 (4%)
Hemorrhoidal thrombosis	2 (8%)	1 (4%)
Complete wound healing (week) *	7 (6-8)	8 (6-9)

* Values are median (IQR). VAS, visual analogue scale

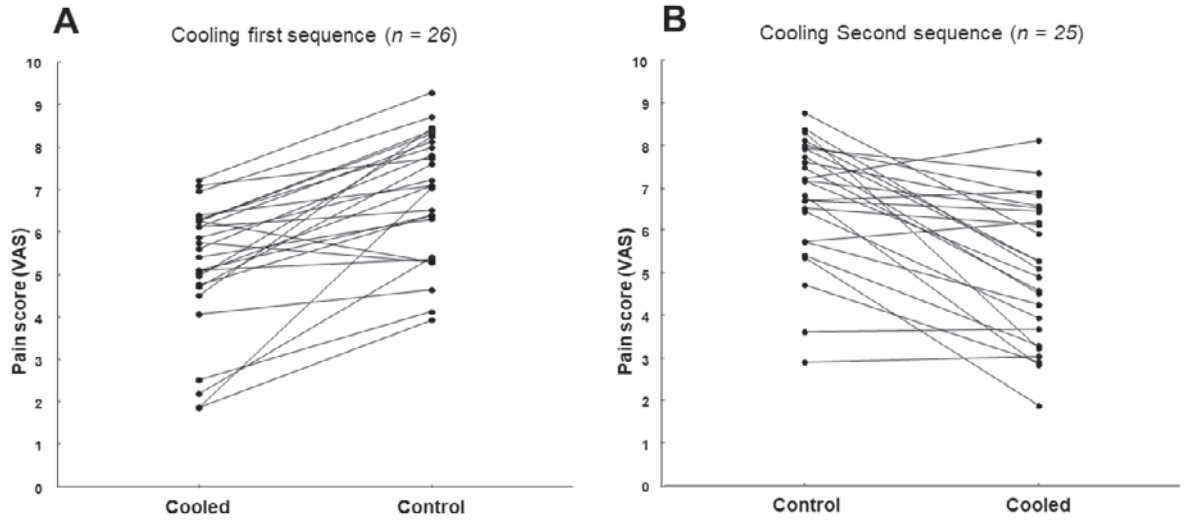

Figure 3. Paired data for individual VAS scores between cooled and control areas shown at a cooling-first sequence and b cooling-second sequence.

the authors strongly recommend pre-cooling because the procedure has the advantages of being easy to perform, inexpensive, and safe (i.e., without side effects such as frostbite). The only observed shortcoming of pre-cooling was that some patients may not be able to withstand the specified cooling time, as evidenced by the 3 patients who could not tolerate 2 minutes of the procedure.

Several clinical trials have been conducted to evaluate the efficacy of pre-cooling in the setting of LA injection, all of which demonstrated the effectiveness of pre-cooling[1-3]. All of those studies were randomized controlled trials, yet none adopted a crossover study design. To our knowledge, this study is the first crossover trial in this field. As the use of a crossover design enables controlling for variability between patients by comparing VAS scores for each patient, more reliable results can likely be obtained from this type of

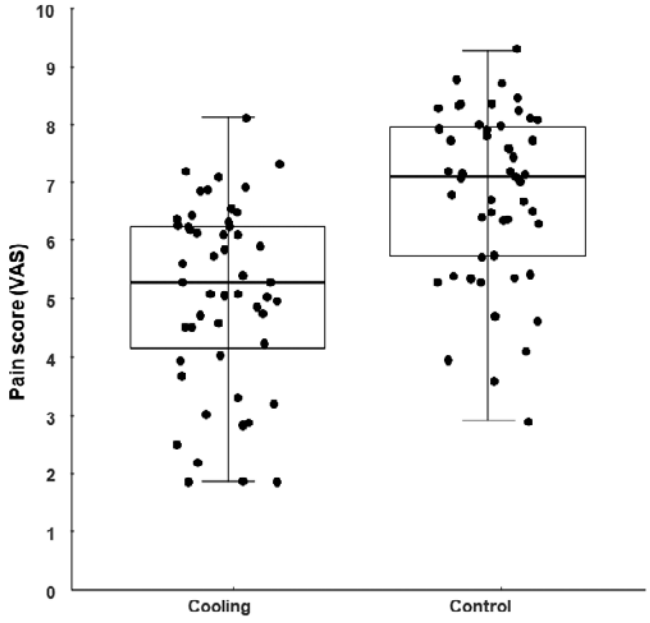

Figure 4. Scattered box plots for VAS scores between cooled and control areas are shown. Bold lines = Median scores, Boxes = Interquartile ranges, Error bars = 95% confidence intervals.

study. However, caution should be exercised in comparing the results of this study to those of prior studies because of differences in pre-cooling times, cooling locations, and needle sizes across studies. In previous studies, the pre-cooling time was either 2 minutes or 5 minutes[2,3]. The cooling locations used in other studies included the face, upper extremity, and inguinal region[3]. Needle sizes in prior studies varied from 27-gauge to 21-gauge[1].

The pre-cooling method described in this study has been used for many years and is not new. Mechanisms of action that have been proposed to explain the amelioration of pain that is associated with pre-cooling include reduction in local circulation[6], altered peripheral nerve conduction velocity[7], and reduction in muscle spasm[8]. However, the exact mode of effect in pre-cooling remains unknown.

This study has several limitations. First, we could not provide the intervention in a blinded manner; however, to minimize potential biases, patients were not informed of the effects of pre-cooling. Second, there is little knowledge regarding optimal waiting (control) time. The estimated carryover effect was rather small compared to the effect of pre-cooling; a 2-minute waiting (control) time was considered

Table 3. Linear Mixed-Effects Model Analysis for VAS Score.

	Estimate	95% CI	*P* value
With pre-cooling (ref: without pre-cooling)	−1.71	−2.11 to −1.31	< 0.001
Male (ref: female)	−0.17	−0.96 to 0.61	0.676
Age (+ 10-year increment)	−0.21	−0.52 to 0.10	0.203
Phase II (ref: phase I)	0.00	−0.40 to 0.40	0.992

VAS, visual analogue scale; CI, confidence interval; ref, reference group

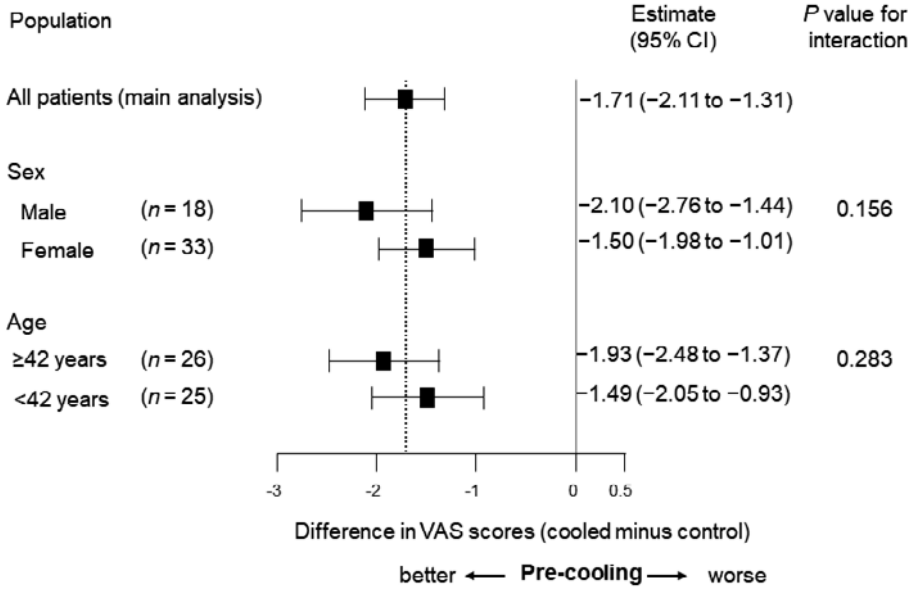

Figure 5. Forest plot of estimated mean VAS score differentials between areas with pre-cooling and those without pre-cooling, from the main and subgroup analyses.

sufficient for the cooling effect to be washed out. Moreover, it is not realistic to use a longer waiting (control) time (e.g., 30 min or 1 h) when the patient is on a surgical table. Third, this trial was conducted at a single center, which may introduce some selection bias.

In conclusion, robust statistical analyses in this study demonstrated that pre-cooling is an effective technique to reduce pain associated with LA injections in hemorrhoidectomy. It is recommended that clinicians should spend 2 minutes conducting pre-cooling before initiating LA injections.

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Conflicts of Interest
There are no conflicts of interest.

Author Contributions
Conceptualization, TY, YI, HY, TI, RK & AS; Methodology, YI, TI & AS; Literature search, TY & YI; Data synthesis, TY, YI & TI; Statistical analysis, TY & YI; Draft preparation, TY & YI; Draft review and revisions, TY, YI, HY, TI, RK & AS. All authors have read and agreed to the published version of the manuscript. TY & YI contributed equally.

Approval by Institutional Review Board (IRB)
This study was approved by the Ethical Committee of Osaka City University Graduate School of Medicine (Approval no. 2021-237).

Trial Registration Number
jRCT1051210201 (Japan Registry of Clinical Trials)

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Supplementary Files

Supplementary File 1.
Supplementary File 2.
Supplementary File 3.
Supplementary File 4.
Supplementary File 5.
Please find supplementary file(s);
http://dx.dor.org/10.23922/jarc.2024-002