Original Article

Double-blind, Randomized, Placebo-controlled Trial to Determine the Efficacy of Eutectic Lidocaine/Prilocaine (EMLA) Cream for Decreasing Pain During Local Anaesthetic Infiltration for Out-patient Haemorrhoidectomy

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OBJECTIVE: The study was undertaken to evaluate the efficacy of eutectic lidocaine/prilocaine (EMLA) cream for decreasing pain during local anaesthetic infiltration for outpatient haemorrhoidectomy.

METHODS: Ninety-eight patients were randomly assigned either to receive EMLA or placebo. The creams were applied 45 minutes prior to injection of a lidocaine/bupivacaine mixture using a diamond-shaped perianal block. All participants were blinded to the specific medication received. They were asked to rate pain and levels of acceptability using a pre-validated pain scale and questionnaire.

RESULTS: There were 49 patients in each group. The baseline characteristics between the two groups were similar. Forty patients (82%) in the EMLA group and 42 patients (86%) in the placebo group reported only mild pain during injection and infiltration of the lidocaine/bupivacaine mixture. The mean rank pain scores were 49.11 and 48.89, respectively ($p = 0.886$, not significant).

CONCLUSION: While outpatient haemorrhoidectomy under local anaesthesia was generally well tolerated, there was no statistically significant difference between EMLA cream and placebo for decreasing pain during anaesthetic infiltration. (*Asian J Surg* 2002;26(1):26–30)

Introduction

The efficacy of local anaesthesia for outpatient haemorrhoidectomy has long been established both in the local and foreign literature. The technique has been proven reliable, safe and inexpensive. Furthermore, it allows for early ambulation and discharge after surgery.[1–5] This is particularly important for busy outpatient departments where concerns about serving an increasing volume of patients must be balanced by cost-containment. In our institution, the number of ambulatory haemorrhoidectomy cases often is limited by the efficiency of the anaesthetists in giving regional anaesthesia. Our division, therefore, decided to implement a policy whereby more patients undergoing outpatient haemorrhoidectomy be treated under local anaesthesia, to be given by the surgeons themselves.

Unfortunately, pain and discomfort often accompany the injection and infiltration of local anaesthesia into the perianal area. In order to avoid this, Nivatvongs described a different technique, wherein the initial infiltration of the anaesthetic is done intra-anally, above the dentate line.[6] However, this technique is difficult for surgical residents to perform and has not gained widespread acceptance. A more common practice is to sedate the patient prior to the infiltration of local

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anaesthesia, but this requires intravenous cannulation and closer monitoring of the patients. Others advocate alkalinizing the anaesthetic solution with sodium bicarbonate, claiming that the acidic nature of the anaesthetic is the main reason for the pain during infiltration.[7] We tried these methods, but our experience shows that they are not always effective, and that some patients still suffer pain during infiltration of the local anaesthetic.

A eutectic mixture of lidocaine and prilocaine (5%, EMLA) cream (AstraZeneca, Sodertalje, Sweden) is the first topical anaesthetic developed that penetrates intact skin. The efficacy of EMLA for the treatment of pain during cutaneous procedures such as biopsies, dermal testing, intravenous cannulation and spinal taps has been well established in several randomized controlled trials and systematic reviews.[8–14] The usual adult dose is 2 to 5 g under an occlusive dressing for 20 to 120 minutes prior to the procedure. Some authors have demonstrated that the minimal effective application of EMLA is 45 minutes.[15]

The evidence for efficacy of EMLA in the literature prompted us to speculate on its usefulness in decreasing the pain during infiltration of local anaesthesia for outpatient haemorrhoidectomy. Only one study using EMLA for these procedures has been performed, but this was a randomized trial comparing general anaesthesia to EMLA with local anaesthesia.[16] It did not evaluate EMLA versus placebo. The aim of this study was to determine the effectiveness of EMLA 5% cream for decreasing pain during injection of local anaesthesia in adult patients undergoing elective, outpatient haemorrhoidectomy.

Patients and methods

This study was a randomized, double-blind, placebo-controlled, parallel-group clinical trial, with prior approval from our Institution's Ethics Review Board. Voluntary, written, informed consent was obtained from all patients prior to enrolment and allocation. Ninety-eight patients with symptomatic grade III or IV internal haemorrhoids, mixed haemorrhoids, and/or external haemorrhoids scheduled for elective outpatient surgery were recruited into the study. Sample size calculations were based on estimated group pain score means of 2.0 for group 1 (experimental group receiving EMLA) and 3.5 for group 2 (control group receiving placebo), and a within-group standard deviation of 2.5, with an estimated sample size of 49 participants per group. Only patients between 18 and 65 years of age with voluntary, written, informed consent to participate in the study were included. Patients with known allergy to any of the study medications and those with moderate to severe co-morbid conditions such as cardiac disease, hypertension, renal failure, diabetes, immunocompromised conditions and pregnant women were excluded from the study. Allocation was through simple randomization using a table of random numbers, which were then sealed in envelopes and opened just before the procedure.

The creams containing either EMLA or placebo were applied at least 45 minutes before the scheduled operation. This was done by an assigned co-investigator, with the patients lying in the left lateral decubitus position. Five grams of EMLA 5% cream was applied to the patient's perianal area for the experimental group, and 5 g of commercially available white moisturizing cream was applied to patients in the control group. The patients were blinded as to what was applied. A 20 x 20-cm plastic occlusive dressing was then taped over the area, and the patients were asked to sit in the waiting area. Just prior to surgery, the patients were again placed in the left lateral decubitus position and the cream was wiped off to make sure the surgeon was blinded as to which cream was applied.

The local anaesthetic was composed of 10 mL of 2% lidocaine, 10 mL of 0.5% bupivacaine, 3 mL of sterile water, 2.5 mL of $NaHCO_3$ and 0.25 mL 1:10,000 epinephrine solution. It was injected subcutaneously by the surgeon using a 30-gauge needle initially, then deep into the anal submucosa and sphincters using a longer 25-gauge needle. The infiltration technique was standardized, using the commonly practised diamond-shaped perianal block. Approximately 10 to 12 mL of local anaesthetic was given on each side, and the surgeon made sure that the infiltration was done slowly, taking approximately 5 minutes to complete. No sedatives were given. The haemorrhoidectomy was performed in the jack knife position, using the open Milligan-Morgan technique. The patients were discharged immediately after the surgery if no serious problems were noted. They were subsequently seen at the outpatient clinics for weekly follow-up for 4 weeks.

Baseline data were recorded and included the variables of age, gender and type of haemorrhoids. Outcomes were measured using two standard questionnaire forms, one for the patients and the other for the surgeons. The rating scales ranged from 0 (no pain/very satisfied) to 5 (severe pain/extremely unsatisfied). The questionnaires were pilot-tested and validated by 12 patients and 12 surgeons prior to the start of the study. An assigned co-investigator who was present throughout the procedure administered the questionnaires. The patients were asked to rate the pain experienced during local anaesthetic infiltration using an ordinal visual pain scale

right after infiltration. After the surgical procedure, the patients were then asked to answer the remaining portions of the questionnaire. The surgeons also answered their corresponding questionnaires after the procedure. The primary outcomes measured were the patients' assessment of pain after infiltration of anaesthesia. Secondary outcomes included patients' assessment of pain after haemorrhoidectomy, satisfaction with the procedure and acceptability of the cream applied. Other secondary outcomes included the surgeon's assessment of the presence or absence of the anal wink reflex during anaesthesia infiltration, plus satisfaction and acceptance of using the cream for the procedure.

Data were encoded into the EPI INFO 2000 programme for Windows (Centers for Disease Control and Prevention, Atlanta, Georgia, USA). Statistical analysis included the Mann-Whitney U-test for the non-parametric ordinal visual scales, and 2 x 2 tables, Chi-square and Fisher's exact test for the nominal data, as deemed appropriate. Dropouts or withdrawals were to be analyzed in the groups to which they were allocated. Hypotheses were tested at a level of significance of 0.05 (two-tailed).

Table 1. Baseline characteristics of patients in the eutectic lidocaine/prilocaine (EMLA) and placebo treatment groups

Patient characteristics	EMLA (n_1=49)	Placebo (n_2=49)	*p* value
Sex			
Male	29 (59.2%)	27 (55.1%)	
Female	20 (40.8%)	22 (44.9%)	0.68 (NS)
Age (mean)	33.49	36.96	0.15 (NS)
Type of haemorrhoids			
External	4 (8.2%)	2 (4.1%)	
Internal	12 (24.5%)	15 (30.6%)	
Mixed	32 (65.3%)	32 (65.3%)	0.8 (NS)
No information	1	0	
Grade of haemorrhoids			
I	3 (6.1%)	1 (2.1%)	
II	9 (18.4%)	16 (12.2%)	
III	3 (6.1%)	5 (10.2%)	
IV	32 (65.3%)	33 (67.3%)	1.0 (NS)
No information	2 (4.1%)	4 (8.1%)	
Duration of infiltration in seconds (mean)	284.28	295.41	0.79 (NS)

NS = not significant.

Results

Ninety-eight patients consented to undergo outpatient haemorrhoidectomy under local anaesthesia during the period from July 2000 to January 2001. Forty-nine patients each were randomly assigned to the experimental EMLA (group 1) and placebo control (group 2) groups. The two groups were similar in terms of gender distribution, mean age, types and grades of the haemorrhoids and mean duration of anaesthetic infiltration (Table 1).

The local anaesthetics were generally well tolerated, with 40 patients (82%) in group 1 and 42 patients (86%) in group 2 reporting either mild or no pain during infiltration, with a relative risk of developing severe pain at 1.29 (95% confidence interval (CI), 0.52, 3.18). One patient in group 2 had to be sedated due to persistent muscle spasm and bleeding, while another was converted to a regional block due to persistent pain. After the haemorrhoidectomy, 44 patients (90%) in group 1 and 42 patients (86%) in group 2 reported mild to no pain at all. In both treatment groups, 43 patients (88%) and 44 surgeons (90%) would recommend the same procedure to other patients.

As assessed by the patients, there was no statistically significant difference between the mean ranks of the two groups, particularly in terms of pain scores after anaesthetic infiltration and after haemorrhoidectomy, and satisfaction levels with the cream and the procedure as a whole. Thirty patients (61%) in group 1 and 33 patients (67%) in group 2 exhibited the anal wink reflex during infiltration, but this was not statistically significant. There was also no statistically significant difference in the comfort and satisfaction rankings of surgeons for both groups (Tables 2 and 3).

Discussion

Haemorrhoidectomy under local anaesthesia is safe, reliable and inexpensive.[1,3] The procedure, performed under local anaesthesia, decreased hospital stay and costs, and avoided potential anaesthetic side-effects such as nausea, vomiting, headache, and others. In this study, the procedure was generally well tolerated, with the majority of patients having nil to mild pain during anaesthetic infiltration and immediately after the operation. Most of the study participants were willing to undergo the same procedure again if necessary. They also indicated that they would recommend its use in other patients.

A growing familiarity with the technique among our surgery residents, and greater acceptability by the patients, has allowed us to increase the number of haemorrhoidectomies that we perform in our outpatient department (Figure).

The number of haemorrhoidectomies done under local anaesthesia rose from a low rate of 4.9% prior to July 2000, to 52.1% during the 6-month study period, and then finally

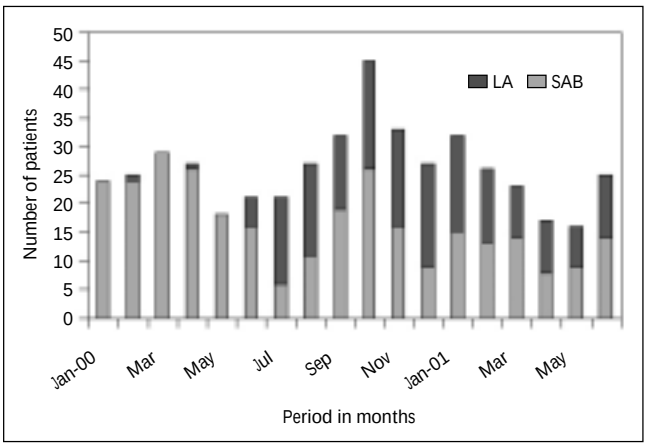

Figure. Outpatient anorectal surgery at the Philippine General Hospital. LA = local anaesthesia; SAB = subarachnoid block.

settled down to a fairly constant rate of 47.5% after the study period. At present, the procedure has become part of our standard management, particularly in our setting where inefficiencies in providing anaesthesia exist.

With an expected increase in the number of haemorrhoidectomies done under local anaesthesia, we wanted to find out if using EMLA cream would further decrease the pain associated with anaesthetic infiltration. Favourable findings from this study would have provided a basis for utilizing EMLA in our treatment protocols for outpatient surgery. However, our results do not show any significant benefit to using the topical anaesthetic. Although this runs counter to many other studies on EMLA, there have been a few randomized trials that have also shown no significant difference between EMLA and placebo.[17,18]

We can only hypothesize why EMLA was not as effective in this study. For example, it may be argued that 45 minutes is too short a period of application. Early in the protocol development, the authors decided on the 45-minute application time because this duration had already been established in previous studies.[15] Furthermore, a period longer than that may have been impractical in the outpatient setting where volume and efficient turnover of cases is a continuing concern.

The efficacy of EMLA in the perianal area requires further study. There is a question of whether absorption of the topical anaesthetic is possibly hindered by the natural pH gradient in

Table 2. Table for non-parametric ordinal data

	EMLA (n_1 = 49)	Placebo (n_2 = 49)	Mann-Whitney U statistics	*p*-value (2 tailed)
I. Assessment by patient (mean)				
Pain scores after infiltration of anaesthetic	1.47	1.37	1181.5	0.886 (NS)
Pain scores after haemorrhoidectomy	0.9	0.8	1158.5	0.745 (NS)
Satisfaction with the anaesthetic cream	1.47	1.49	1113.5	0.503 (NS)
Satisfaction with the whole procedure	1.12	1.04	1185.5	0.909 (NS)
II. Assessment by surgeon (mean)				
Comfort levels of patient during infiltration of anaesthetic	2.45	2.43	1178.0	0.855 (NS)
Satisfaction with anaesthetic	1.98	1.88	1103.0	0.424 (NS)

NS = not significant.

Table 3. Table for dichotomous responses

	EMLA (n_1 = 49)		Placebo (n_2 = 49)		*p*-value (associated with Fisher's exact test)	RR (95% CI)
	Yes	%	Yes	%		
I. Assessment by patient						
Less pain	35	71.4	34	69.4	1.000 (NS)	1.017 (0.7,1.5)
Acceptable waiting time	38	77.6	35	71.4	0.769 (NS)	0.965 (0.7,1.3)
Recommends procedure	43	87.8	43	87.8	1.000 (NS)	1.000 (0.8,1.3)
II. Assessment by surgeon						
Anal wink (+)	30	61.2	33	67.3	0.674 (NS)	1.100 (0.7,1.7)
Less pain	38	77.6	35	71.4	0.633 (NS)	0.921 (0.6,1.3)
Recommends procedure	44	89.8	44	89.8	1.000 (NS)	1.000 (0.8,1.3)

CI = confidence interval; NS = not significant.

that region, or by the thickened epithelium constantly exposed to chemical irritants. The ability to apply and maintain the EMLA cream and its corresponding occlusive dressing around the anus and between the buttocks, despite movements while walking, or compression while sitting, are issues that also need to be resolved.

Ho et al did the only other study on EMLA for haemorrhoidectomy that we found after a thorough Medical Subject Headings search using MEDLINE™ and Cochrane.[16] In this randomized clinical trial, they report that the topical anaesthetic cream with local anaesthesia did not have any significant difference when compared to general anaesthesia in terms of operating time, postoperative pain, nausea or vomiting, pain-free interval after operation, analgesic requirements, patient's satisfaction with the method of anaesthesia, postoperative oxygen saturation and pulse rate. They concluded that EMLA with local anaesthesia was just as effective as general anaesthesia. Ten grams of EMLA were used for each patient in their study. The perioperative area was then covered by specially prepared gauze impregnated with paraffin. The patients were also made to rest lying on their side. This is quite different from the technique that we used, and may, theoretically, be more effective. Nonetheless, the study by Ho et al was hampered by its small sample size (27 in the EMLA group, 26 in the GA group). They reported that 18 patients in the EMLA group (67%) experienced only mild or no pain during injection of the anaesthetic. This proportion is even fewer than the 86% of patients who had mild to no pain in the placebo group in our study. Furthermore, Ho et al evaluated EMLA and local anaesthesia versus general anaesthesia. They did not evaluate whether or not EMLA itself was effective, which would have required comparing it to placebo, all other variables being equal. Based on our data, our contention is that the pain associated with the infiltration of local anaesthesia is well tolerated and acceptable to the majority of patients and that adding EMLA does not confer any significant benefit.

While outpatient haemorrhoidectomy under local anaesthesia was generally well tolerated and acceptable in this study, with most patients experiencing only mild pain, there was no statistically significant difference between EMLA and placebo in decreasing pain during anaesthetic infiltration.

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