

Postoperative Intramuscular Dextromethorphan Injection Provides Postoperative Pain Relief and Decreases Opioid Requirement after Hemorrhoidectomy

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Background: Previous studies have shown that dextromethorphan (DM) produces an analgesic/antihyperalgesic effect. This study was designed to examine whether postoperative DM intramuscular (IM) injection could reduce post-hemorrhoidectomy pain.

Methods: At the end of surgery, patients in the study group (n = 30) were given an intramuscular injection of 40 mg DM and 20 mg chlorpheniramine (CPM) while in the control group (n = 30), the patients were given intramuscular 20 mg CPM only. Pethidine (1 mg/kg, IM) was prescribed for postoperative pain relief if required. The time to first pethidine injection, total pethidine consumption, worst pain score, and pethidine-related side effects were recorded for 48 h postoperatively.

Results: The time from the end of operation to the first pethidine injection was 5.4 ± 1.6 h and 17.8 ± 3.7 h ($P = 0.006$) in the control group and the study group, respectively. Total pethidine consumption was 139.5 ± 11.5 mg and 77.5 ± 12.2 mg ($P < 0.001$) in the control group and the study group, respectively. The worst VAS score was 7.5 ± 0.2 and 7.1 ± 0.2 ($P = 0.09$) in the control and the study groups, respectively. The number of patients who required pethidine injection was 29 and 21 ($P < 0.005$) in the control and the study groups, respectively. The number of patients who suffered pethidine-related side effects was 7 and 1 ($P < 0.025$) in the control and the study groups, respectively.

Conclusions: We found that intramuscular DM given at the end of operation could provide good postoperative pain relief and decrease the pethidine requirement after hemorrhoidectomy.

Key words: *Dextromethorphan. Hemorrhoids. Pain: postoperative.*

Post-hemorrhoidectomy pain is feared by many patients. Perianal infiltration with local anesthetic is the most popular technique for hemorrhoidectomy since it rarely causes complication and costs less; it also offers immediate pain relief. However, because its effect is short-lived, it does not sustain a pain relief very long after surgery.¹ Therefore, postoperative non-steroidal

anti-inflammatory drugs (NSAIDs) and opioids are prescribed for continuous pain relief after hemorrhoidectomy, but still not satisfied. NSAIDs have been shown to be as effective as but safer than opioid analgesics for post-hemorrhoidectomy pain relief,² but may cause bleeding by inhibiting platelet function and prolonging bleeding time.³ Therefore, their use in patients who are at risk of bleeding should be prohibited.⁴ Further, the narcotic-related side effects including nausea, constipation, and urinary retention may prolong hospital stay.⁵

Postoperative pain is a multifactorial symptom involving ongoing sensory signals generated from the damaged tissue and injured nerves, by the transmission of which the central nociceptors are sensitized. Human stu-

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dies have shown that N-methyl-D-aspartate (NMDA) receptor antagonists inhibit the central nociceptive neurons sensitization, thus, attenuating neuropathic and post-operative pains.⁶⁻¹⁰ In experimental study, NMDA receptors have been demonstrated to play an important role in neuronal wind-up, thus, by blocking NMDA receptors activation it may prevent nociceptor central sensitization.¹¹ In laparotomy, dextromethorphan (DM) reduces the intraoperative morphine requirement and thus, it is necessary to go further to examine whether post-operative administration of DM is equally effective. Recently, we have also found that DM provides a weak analgesic/antihyperalgesic effect in laparoscopic cholecystectomy (LC).¹² Therefore, the purpose of this study was to examine whether DM administered at the end of surgery could prolong the analgesic effect of local anesthetic, thus, improving the quality of post-hemorrhoidectomy pain relief and reducing the need and side effects of narcotic.

Materials and Methods

With institutional approval and patient written informed consent, sixty ASA I-II patients of both sexes, scheduled for hemorrhoidectomy (Grade III-IV) were randomly divided into control and study groups. Patients who had received opioids or NSAIDs within one week and other medications that could interact with dextromethorphan, such as quinidine, flecainide, mexiletine, fluoxetine, amitriptyline, nortriptyline, and propafenone were excluded. At the end of surgery, patients in the study group ($n = 30$) were given an intramuscular injection containing 40 mg DM and 20 mg chlorpheniramine (CPM). Patients in the control group ($n = 30$) were likewise given an intramuscular injection containing only 20 mg of CPM. The injection of CPM in the control group was to counter-balance the CPM effect in the study group in which the DM injection used contained CPM (5 mg in each 10 mg of DM) made to the specifications.

All patients received local anesthesia in the Jack-knife position with 10 ml 2% lidocaine thinned by 30 mL normal saline containing 0.4 mg of epinephrine. Modified Whitehead procedure was selected for hemorrhoidectomy. Standard vital signs monitoring included electrocardiogram, non-invasive blood pressure and pulse oximetry. No opioids or NSAIDs were given during operation. All patients were taught how to use the visual analog scale (VAS) (0-10 cm, 0 = no pain and 10 = worst pain imaginable) to score the pain intensity the day before surgery. Pethidine (1 mg/kg, IM) was prescribed for postoperative pain relief if VAS > 3. We recorded the time from the administration of the assigned drug to the first pethidine injection, the worst pain score, total pethi-

dine consumption, and pethidine-related side effects (such as nausea, vomiting, dizziness, hot flushes, drowsiness, heartburn, and headache) up to 48 h. The study was designed on a double-blind basis and all the assessments were carried out by a resident anesthesiologist who was blind to the study. Side effect if any was treated with appropriate medication, if necessary.

Most data were presented as mean \pm SEM and statistically analyzed with Student's *t*-test. The Log-rank test was used to evaluate the statistical difference of the time from the injection of the assigned drug to the first pethidine injection. Pain scores were analyzed using the Mann-Whitney *U* test. The χ^2 test was used to evaluate the statistical differences of meperidine requirements and side effects. *P* value < 0.05 was considered to be of statistical significance.

Results

There were no demographic data and surgical time differences between the two groups (Table 1). The average time from the end of operation to the first pethidine injection was significantly longer in the study group (17.8 ± 3.7 h) than in the control group (5.4 ± 1.6 h, $P = 0.006$; Table 2). The total pethidine consumption was significantly less in the study group (77.5 ± 12.2 mg) than in the control group (139.5 ± 11.5 mg, $P < 0.001$; Table 2). As to the worst pain score in those patients asking for pain relief with pethidine, there was no difference noted on the worst pain score between the control group (7.5 ± 0.2) and the study group (7.1 ± 0.2 , $P = 0.09$). Most of the worst pain scores were reported at the time of pethidine injection, particularly at the first injection (Table 3). However, a statistically significant reduction in the number of patients who required pethidine injection was noted in the study group (21 vs. 29, $P < 0.005$; Table 2). Seven and one patients suffered from the pethidine-related side effects (nausea, vomiting, dizziness and

Table 1. Demographic Data

	Control (n = 30)	Study (n = 30)
Age (yr)	43.2 \pm 2.3	39.6 \pm 2.7
Sex (M/F)	18/12	20/10
Weight (kg)	62.0 \pm 2.0	59.8 \pm 1.8
Height (cm)	164.9 \pm 1.5	163.3 \pm 1.4
Operation duration (min)	40.3 \pm 1.8	44.2 \pm 2.1

The control group patients received CPM 20 mg IM, while in the study group patients received 40 mg DM containing 20 mg CPM IM given at the end of surgery. Data are presented as mean \pm SEM. There are no significant differences between the two groups.

Table 2. Postoperative Analgesia, Incidence of Side Effects and Pethidine Requirement

	Control (n = 30)	Study (n = 30)
Time to 1st pethidine injection (hr)*	5.4 ± 1.6	17.8 ± 3.7 ^a
Total pethidine consumption (mg) [†]	139.5 ± 11.5	77.5 ± 12.2 ^b
Pethidine requirement ^{††}	29	21 ^c
Pethidine-related side effects ^{††}	7	1 ^d

*The statistic method was Log-rank test; the data was presented as mean ± SEM; a: $P = 0.006$. [†]The statistic method was Student's t test; b: $P < 0.001$. ^{††}The statistic method was χ^2 test; c: $P < 0.005$; d: $P < 0.025$. Side effects included nausea, vomiting, dizziness and headache. Pethidine-related side effects and pethidine requirement represent patients who had any one of these side effects or required pethidine injection for pain relief.

headache) in the control and the study groups respectively ($P < 0.025$; Table 2). The VAS scores were less than 3 in those patients who did not require pethidine in both groups. There were no DM and CPM-related side effects (such as dizziness, hot flushes, tremor, drowsiness, heartburn, nausea, and vomiting) seen within the 2-hr observation in the postoperative recovery room (data not shown).

Discussion

The present study showed that patients who received postoperative DM injection obtained good postoperative pain relief as reflected by both longer time from its administration to the first pethidine injection and less total pethidine consumption. Furthermore, a significant reduction in the number of patients who required further pethidine injection for pain relief was also noted in DM group patients. A significant attenuation of pethidine-related side effects was observed in the study group. Irrespective of whether receiving DM injection or not, all the patients who asked for the first dose of pethidine rated the intensity of pain with similar scores; it reflected that all these patients felt severe pain when asked for pethidine injection because we had suggested to patients before surgery that a pain with a score more than 3 was of clinical significance. The results suggested that all pa-

tient followed our advice to ask for treatment of pain.

Evidence from animal models and clinical studies has demonstrated that DM can alleviate some types of pain, such as neuropathic, thermal and postoperative pains by inhibiting the NMDA receptors. Tal *et al.*¹³ and Mao *et al.*¹⁴ found that DM could reduce the neuropathic pain syndromes resulting from the peripheral nerve injury in rats. Klepstad *et al.*¹⁵ reported that DM (125 mg/day) reduced post-herpetic neuralgia in a double-blind trial. Moreover, Ilkjaer *et al.*¹⁶ demonstrated that DM 60 and 120 mg reduced the magnitude of secondary hyperalgesia to pinprick, but had no influence on primary hyperalgesia and pain of prolonged noxious thermal stimulation. In a double-blind, randomized, placebo-controlled crossover design where six volunteers were given oral doses of DM 15, 30, 45 mg, and placebo, Price and colleagues found that DM reduced slow temporal summation of electrically and thermally evoked second pain (a correlation with wind-up) in a dose-dependent manner.¹⁷ Grace *et al.*¹⁸ demonstrated that oral DM reduced intraoperative morphine requirement in laparotomy. In our previous study, we found that intramuscular DM during laparoscopic cholecystectomy, provided an analgesic effect.¹² The result of the study is consistent with our inference that DM provides an analgesic effect after hemorrhoidectomy.

However, these positive results still have been the subject of controversy. Kauppila *et al.*¹⁹ found that DM 100 mg (oral) did not attenuate the pain produced by topical application of capsaicin or ischemia. McQuay *et al.*²⁰ also failed to demonstrate that DM had any analgesic effect on neuropathic pain syndromes at dosage of either 40.5 mg or 81 mg daily in a 10 days' observation. Moreover, McConaghy *et al.*²¹ found that two doses of 27 mg DM given before operation and three further doses given 8, 16 and 24 h after operation, did not produce any benefit for postoperative pain relief. The negative results of those reports narrated above might be due to the fact that the dosages of DM were probably too small in comparison with ours. The bioavailability of oral DM is only about 10% of that of intravenous DM,²² while the bioavailability of intramuscular DM is similar to intravenous DM. Moreover, the onset of intramuscular DM is almost as rapid as IV DM in our study. Nelson *et al.*²³ found that DM in higher oral dose of 381 mg/day which is compatible to our intramuscular dose of 40 mg did provide a satisfactory pain relief for painful diabetic peripheral neuropathy.

Local anesthetic infiltration which prevents pain impulses from reaching the spinal cord avoids initiation of neuronal wind-up. It can also block the feedback amplification of the neuronal pain signal at the spinal cord level and serves to lighten the physiologic response to pain.²⁴ Blocking NMDA receptors has been demonstra-

Table 3. Visual Analog Pain Scores

	Control (n = 29)	Study (n = 21)	P value
At first pethidine injection	7.5 ± 0.2	7.1 ± 0.2	0.09

Data are expressed as mean ± SEM. There is no difference at pain scores of the first pethidine injection between two groups. The statistic method was Mann-Whitney U test.

ted to prevent neuronal wind-up and spinal nociceptive neurons hyperexcitability.^{11,25} Besides, the NMDA antagonists have been proved to be particularly effective in preventing the consequences of noxious afferent input resulting from ongoing damage of neurons.²³ In the present study, DM, being a NMDA antagonist, might enhance the local anesthetic effect by blocking the NMDA receptors. Many experimental studies have indicated that a blockade of the NMDA receptors done before the noxious stimuli enter the central nervous system is more effective than one performed after.^{26,27} Whether the administration of DM before surgery may enhance the preemptive effect of local anesthetic infiltration warrants further investigation.

We conclude that intramuscular DM injection, following local lidocaine infiltration, could reduce the intensity of postoperative pain, decrease the pethidine consumption, and delay the need of pethidine after hemorrhoidectomy.

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痔瘡手術後給予 Dextromethorphan 肌肉注射 可以降低術後疼痛及類鴉片藥物的需求

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背景：痔瘡切除術後的疼痛常令病患痛苦難當。最近的研究已顯示在術中注射止咳藥 dextromethorphan (DM)，一種 NMDA 接受器拮抗劑，具有止痛的效果。本實驗的目的是檢測在痔瘡切除術後肌肉注射 DM，是否也具有止痛的效果，以改善痔瘡術後的疼痛並可降低類鴉片類藥物的需求及副作用。

方法：本實驗選擇六十位 ASA I-II 預備要接受痔瘡切除的病人，隨機分為二組。實驗組病人在術後接受肌肉注射 DM 40 mg 和 CPM 20 mg；對照組病人在術後接受肌肉注射 CPM 20 mg。術後病人若要求止痛則給予肌肉注射 pethidine (1 mg/kg)。術後我們觀察 48 小時，並記錄病人第一次要求注射 pethidine 的時間、pethidine 的總消耗量、最痛的分數及 pethidine 引起的副作用等。

結果：第一次 pethidine 注射的時間在對照組和實驗組分別為 5.4 ± 1.6 和 17.8 ± 3.7 小時。Pethidine 的總消耗量則分別為 139.5 ± 11.5 (對照組)和 77.5 ± 12.2 (實驗組)毫克。需要 pethidine 止痛的人數分別為 29(對照組)和 21(實驗組)人。而有注射 pethidine 的病人其 VAS 最痛的分數分別為 7.5 ± 0.2 (對照組)和 7.1 ± 0.2 (實驗組)。至於 pethidine 引起的副作用則分別為 7(對照組)及 1(實驗組)人。

結論：我們發現術後肌肉注射 DM 可降低痔瘡術後的疼痛、並延後第一次 pethidine 注射的時間，且 pethidine 的消耗量及 pethidine 引起的副作用均明顯的降低。

關鍵詞：Dextromethorphan。痔瘡。術後疼痛。