

Original Article

An Evaluation of the Efficacy and Safety of Transnasal Butorphanol for Post-hemorrhoidectomy Pain Relief

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Key Words

Opioid;

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Purpose. Postoperative pain is the major patient complaint after hemorrhoidectomy, and adequate analgesia is imperative. Our purpose was to compare the analgesic properties and efficacy of transnasal butorphanol with meperidine.

Methods. Forty patients who underwent hemorrhoidectomy were enrolled in the study from October 2006 to October 2007. They were divided randomly into two equal groups. Postoperatively, the butorphanol group received tolfenamic acid (100 mg) every 6 h and butorphanol nasal spray (1 mg) at least every 4 h if in pain. The meperidine group received tolfenamic acid (100 mg) every 6 h and intramuscular meperidine (0.8 mg/kg) at least every 4 h if in pain. Assessment of postoperative pain was made using a visual analogue scale (VAS) from 1 to 10. Medicinal adverse effects such as somnolence, dizziness, nausea and vomiting were recorded. Satisfaction with narcotic efficacy, desire to use this analgesia in the future, if required, and complaints were recorded using questionnaires before discharge.

Results. Twenty-one (52.5%) patients were men and 19 (47.5%) were women. The mean age was 45.20 years in the butorphanol group compared with 43.85 years in the meperidine group. The mean VAS score was 7.12 in the butorphanol group compared with 7.63 in the meperidine group. After analgesia, the mean VAS score was reduced from baseline by 1.93 in the butorphanol group compared with 2.68 in the meperidine group after analgesia ($P = 0.182$). The incidence of somnolence (30%) was higher in the butorphanol group. However, there were no statistically significant differences in adverse effects between the two groups. In addition, most of the patients were satisfied with the butorphanol nasal spray and wished to receive this analgesic in the future, if needed.

Conclusion. Butorphanol nasal spray and meperidine were equally safe and effective for the relief of pain in patients undergoing hemorrhoidectomy. However, the butorphanol nasal spray offers more convenient and effective outpatient usage.

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Butorphanol (Lotus Pharmaceutical Co., Ltd, Taipei, Taiwan) is a synthetic opioid analgesic with

agonist activity for the κ opioid receptor and antagonist activity for the μ opioid receptor.¹ It is indicated

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for the relief of moderate to severe pain when the use of an opioid analgesic is appropriate. It has an analgesic potency 3.5 to 7 times that of morphine.² In addition, it produces less dose-related respiratory depression or physical dependence.¹ Butorphanol nasal spray was approved by the United States Food and Drug Administration in 1992. The transnasal route is an alternative method of administration and provides easier usage than injectable formulations. It provides a rapid onset of pharmacological action, with blood levels peaking 30 to 60 min before those found with oral formulations.^{1,3} Several reports have demonstrated that butorphanol nasal spray is beneficial in treating acute musculoskeletal pain, pain after cesarean sections, migraine headaches and dental surgery.⁴⁻⁷ Patients who receive hemorrhoidectomy always complain of intractable pain, and the need for analgesia after this procedure is well recognized. The objective of this study was to evaluate the safety and efficacy of a butorphanol nasal spray for treating patients with pain after hemorrhoidectomy.

Materials and Methods

After approval of the review boards of Tri-Service General Hospital and receiving each patient's written informed consent, 40 patients (diagnosed with mixed hemorrhoids, grade III) scheduled for hemorrhoidectomy were enrolled for study from Oct 2006 to Oct 2007. Patients were randomly assigned into the meperidine control group ($n = 20$) and the butorphanol group ($n = 20$) using a random number table. Exclusion criteria were American Society of Anesthesiologists (ASA) physical status $> II$, any history of atrophy sinusitis or repeated epistaxis, previous anorectal surgery, thrombosed hemorrhoids, inflammatory bowel disease, hematologic disorders, significant cardiovascular disease, impaired renal function (serum creatinine > 1.5 mg/dL), hepatic disease (twice above the upper normal limit of AST or ALT levels), psychiatric disorder or being unfit for surgery. These criteria were selected because of the risk of altered drug metabolism, absorption and available information on safety.

A standardized heavy station (meperidine 1

mg/kg, midazolam 0.08 mg/kg) and surgical technique (modified Ferguson's hemorrhoidectomy⁸) were prescribed for all patients. Within 6 h after completion of surgery, when the patient became conscious, all patients were given oral analgesia (Tolfenamic acid 10 mg). Afterward, oral analgesia was prescribed regularly every 6 h. If in pain, the patients in the butorphanol group received one spray of butorphanol (1 mg) at least every 4 h, and patients in the meperidine group received intramuscular meperidine (0.8 mg/kg) at least every 4 h.

Assessment of postoperative pain was made using a 10-point subjective visual analogue scale (VAS, 0 = 'no pain' and 10 = 'maximum pain'). Before receiving the first dose of the butorphanol or meperidine, the patient's VAS was recorded as an initial baseline. The efficacy end point was to evaluate any change in VAS score from the baseline, measured at 60 min after analgesia. Any adverse effects of the narcotic medicines such as somnolence, dizziness, nausea and vomiting were recorded. Hospital stay was also recorded. In addition, the patients were asked for their satisfaction with the efficacy of analgesia and to report any adverse effects using questionnaires before discharge.

Demographic information, patient characteristics and VAS scores were compared between groups using Student's *t* or chi-squared tests. Side effects between groups were analyzed using Fisher's exact test. The Wilcoxon rank-sum test was used to compare hospital stay between the groups. $P < 0.05$ was considered statistically significant.

Results

Of the 40 patients, 21 (52.5%) were men and 19 (47.5%) were women. The mean patient age was 45.20 years in the butorphanol group compared with 43.85 years in the meperidine group. The patient demographics were similar between the groups (Table 1). All patients received the same surgical procedure and had similar surgical times ($P = 0.605$). The frequency of using analgesics was 3.05 in the butorphanol group compared with 1.3 in the meperidine group ($P < 0.001$). The VAS scores were similar between groups (Table 2). The mean VAS score was

Table 1. Patient Characteristics

Variable	Butorphanol Group (n = 20)	Meperidine Group (n = 20)	P value
Age (y, mean ± SD)	45.20 ± 13.34	43.85 ± 13.34	0.760
Sex			
Men	10 (50%)	11(55%)	1.000
Women	10 (50%)	9 (45%)	
Weight (kg, mean ± SD)	63.05 ± 10.92	68.20 ± 14.96	0.221
Height (cm, mean ± SD)	164.60 ± 8.05	166.25 ± 8.16	0.524

Table 2. Result

Variable	Butorphanol Group (n = 20, mean ± SD)	Meperidine Group (n = 20, mean ± SD)	P value
Operative Time (min)	47.35 ± 18.55	49.90 ± 11.63	0.605
Frequency of usage of analgesics (times)	3.05 ± 1.64	1.30 ± 0.47	< 0.001
Initial VAS	7.70 ± 2.20	7.90 ± 1.45	0.736
Mean VAS	7.12 ± 2.27	7.63 ± 1.17	0.384
Change of VAS	1.93 ± 2.24	2.68 ± 0.96	0.182
Hospital stay (days)	3.0 ± 0.31	3.05 ± 0.38	0.785

VAS = visual analogue scales

7.12 in the butorphanol group compared with 7.63 in the meperidine group ($P = 0.384$). The mean VAS score was reduced by 1.93 in the butorphanol group compared with 2.68 in the meperidine group ($P = 0.182$). The mean hospital stay was 3.0 days in the butorphanol group and 3.05 in meperidine group. Thus, the analgesic effects were not statistically different between groups.

For medicinal efficacy, several adverse effects were recorded (Table 3). The incidence of patients recording somnolence was higher in the butorphanol group (30%) than in the meperidine group (15%). In the questionnaires, most of the patients were satisfied with the analgesic they received. Fourteen patients in the butorphanol group (70%) preferred to receive this medicine for analgesia in the future, if needed. However, in the butorphanol group, one patient complained of a poor analgesic response, and four patients complained about multiple side effects. Two patients in the meperidine group complained about multiple side effects.

Table 3. Adverse effects

Adverse effect	Butorphanol Group (n = 20)	Meperidine Group (n = 20)	P value
Somnolence	6 (30%)	3 (15%)	0.451
Dizziness	4 (20%)	3 (15%)	1.000
Nausea	3 (15%)	2 (10%)	1.000
Vomiting	2 (10%)	2 (10%)	1.000

Discussion

The butorphanol nasal spray was effective in relieving pain at 60 min after administration. Postoperative pain is one of the major complaints for patients who have received hemorrhoidectomy. Thus, adequate analgesia is important in recovery even after the patient has been discharged. Butorphanol has been available in an injectable form since 1979. Initially, it was prescribed for intravenous or intramuscular administration to avoid the problem of hepatic first-pass metabolism following oral administration.¹ In 1992, a transnasal formulation was developed to avoid the reduced bioavailability via oral administration. Transnasal butorphanol offers greater bioavailability (48-70%) than the sublingual or buccal formulation (5-17%).¹ Compared with the two other formulations, transnasal administration produces higher maximum concentration, rapid absorption and better relief of pain.^{1,9} Moreover, the nasal spray allows self-administration and usage that is more convenient for patients, especially as outpatients. Our result was consistent with previous reports in terms of the efficacy of butorphanol in treating moderate to severe pain. It also confirms previous studies that butorphanol is rapidly absorbed via the nasal mucosa, with onset of analgesia in 15 min and peak activity within 1-2 h.^{1,10} Furthermore, these data also reveal that butorphanol nasal spray was as effective as meperidine for pain relief.

The frequency of usage was significantly higher in the butorphanol group than in the meperidine group (3.05 times versus 1.30, $P < 0.001$). Therefore, the analgesic effects of butorphanol might have been less than meperidine as it was used more frequently. However, the reduction in the VAS pain score was similar in both groups ($P = 0.182$). One possible explanation

is that the transnasal butorphanol was less invasive and more acceptable to patients. Thus, a butorphanol nasal spray could be considered an alternative form of patient-controlled analgesia.

The most frequently reported adverse events of the butorphanol nasal spray are somnolence, dizziness, nausea, vomiting, sweating, lightheadedness and confusion.^{1,11} In the present study, somnolence was obviously more prevalent in the butorphanol group. However, the adverse effects were not significantly different in frequency between groups. In questionnaires, one patient who received the butorphanol nasal spray reported a poor response, but this might have been associated with distressing adverse effects. Hence, to accomplish the maximum benefit of butorphanol nasal spray, the clinician should inform patients about possible adverse effects. Patients must also be alerted to the sedative properties of butorphanol and be cautioned to avoid work such as driving or operating equipment.

This study had several limitations, primarily the small sample size. In addition, the VAS pain scores were subjective, possibly reflecting inadequate instruction or poor patient understanding. Unfortunately, this prevents an exact comparison of the analgesic efficacy of these two medications.

In conclusion, the butorphanol nasal spray was equivalent to meperidine for the relief of pain after hemorrhoidectomy. Moreover, for outpatients, the butorphanol nasal spray offers more convenient use than meperidine.

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原 著

鼻噴劑型 Butorphanol 止痛藥對痔瘡手術後止痛效果及安全性之評估

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目的 痔瘡手術術後，傷口疼痛是病患常見的問題，適當的止痛是必須且重要的。我們比較鼻噴劑型 Butorphanol 止痛藥相對於肌肉注射 Meperidine 對於手術後的止痛效果和安全性，目的在增進術後疼痛控制的品質。

方法 從 2006 年 10 月到 2007 年 10 月，四十位病患接受痔瘡手術的病患，以隨機的方式分為兩組，每組二十人。Butorphanol 組是術後每六小時口服 Tolfenamic acid 100 mg 及疼痛時每四小時間隔給予鼻噴劑型 Butorphanol 止痛藥一噴 (1 mg)。Meperidine 組是術後每六小時口服 Tolfenamic acid 100 mg 及疼痛時每四小時間隔給予肌肉注射 Meperidine 止痛藥 (0.8 mg/kg)。疼痛指數以 VAS 指數作為評估並紀錄藥物的不良反應包含嗜睡、暈眩、噁心及嘔吐，另外在病患出院前給予問卷詢問對藥物的止痛效果滿意度、副作用的反應及後續使用的意願。

結果 病患中 21 位為男性 (52.5%)，19 位為女性 (47.5%)，在 butorphanol 組平均年齡為 45.20 歲，於 meperidine 組平均年齡為 43.85 歲，未給藥前疼痛指數在 butorphanol 組平均為 7.12，於 meperidine 組平均為 7.63，在接受止痛藥治療後，疼痛指數在 butorphanol 組平均下降 1.97，於 meperidine 組平均下降 2.68，並無統計學的差異 ($P = 0.182$)。在 butorphanol 組有較多嗜睡的副作用 (30%)，但在副作用比較上，兩組並無統計學上的差異。另外，於問卷調查中，大多數病患滿意鼻噴劑型 Butorphanol 的止痛效果及方便性，並願意下次繼續接受鼻噴劑型 Butorphanol 止痛藥。

結論 鼻噴劑型 Butorphanol 在痔瘡術後的止痛效果和 meperidine 止痛藥相比，病患的滿意度相似，然而鼻噴劑型 Butorphanol 可以更方便的使用，以達到止痛及減少醫療資源的效果。

關鍵詞 類鴉片止痛藥、Butorphanol、Meperidine、痔瘡手術。