Transnasal Butorphanol for Pain Relief after Uvulopalatopharyngoplasty – A Hospital-based, Randomized Study

Hao-Chun Huang, MD; Li-Ang Lee, MD; Tuan-Jen Fang¹, MD; Hsueh-Yu Li, MD; Ching-Chia Lo, MD; Jo-Hsuan Wu, MD

Background: Nasal spray of analgesic is a novel administration for postoperative pain control. In this study, we assessed the efficacy of transnasal butorphanol (TB) for pain relief following uvulopalatopharyngoplasty (UPPP) in obstructive sleep apnea (OSA) patients, and compared pain alleviation effect to oral mefenamic acid and intramuscular meperidine (M&M).

Methods: A prospective, randomized, open label study was conducted in a tertiary care sleep center. Twelve OSA patients with full consciousness and at least moderate oropharyngeal pain (pain visual analogue scale [VAS] ≥ 4) after UPPP were recruited. They were randomized to receive TB (n = 7) and M&M (n = 5). Oropharyngeal pain was measured by a VAS and the Clinical Global Impression in Severity (CGI-S) and Improvement (CGI-I) at the 12th, 24th, and 72th hours postoperatively. Postoperative pain related morbidities (PRMs) and quality of life in bodily pain (QOL-BP) were also evaluated 72 hours postoperatively. Adverse events incurred by pain treatment were carefully monitored during patients’ hospitalizations.

Results: No major complication occurred throughout the study. Analysis of clinical measures revealed significantly improved VAS (p = 0.04), CGI-S (p = 0.03), and CGI-I (p = 0.02) in the TB group. However, no significant difference (p > 0.05) in the degree of pain relief was found between the two groups, as denoted by aforementioned three variables, PRMs, and QOL-BP.

Conclusions: Administration of TB can significantly alleviate the wound pain after UPPP in OSA patients. This study also confirmed the safety of TB in patients undergoing oropharyngeal surgery.


Key words: butorphanol, pain alleviation, obstructive sleep apnea, uvulopalatopharyngoplasty, postoperative pain

Symptom management options of obstructive sleep apnea (OSA) include body weight reduction, continuous positive airway pressure, oral appliance, and surgery. The decision to intervene is based...
on multiple factors including the patient's degree of morbidity, anatomic levels of obstruction and associated comorbidities. The most commonly applied surgical procedure is uvulopalatopharyngoplasty (UPPP) which increases the retropalatal space. UPPP has been criticized for its low success rate and severe postoperative pain.\(^{(1)}\) Patients usually suffer severe pain, especially during swallowing and consequently result in morbidities and delayed return to normal activities after UPPP.\(^{(2)}\) We have reported that a short-term administration of intravenous ketorolac was superior to the conventional regimen (oral mefenamic acid and intramuscular meperidine) and represented a safe and effective treatment for wound pain.\(^{(3)}\)

Butorphanol, a synthetic opioid agonist-antagonist drug, is a potent narcotic agent and its analgesic potency is 15-23 times greater than that of meperidine.\(^{(4)}\) It can be administrated intramuscularly, intravenously or transnasally to treat moderate to severe pain. The major side effects of butorphanol are drowsiness and dizziness. However, it does not appear to cause dose-related respiratory depression\(^{(5)}\) and seldom causes physical dependence.\(^{(6)}\) Therefore, transnasal butorphanol characters by easy and self administration without problems of injection and parenteral absorption. Accordingly, short-term administration of butorphanol nasal spray may benefit the OSA patients to sufficiently alleviate severe wound pain following UPPP.

Several papers in the literature have described results obtained with transnasal butorphanol.\(^{(7-15)}\) However, our literature review located only two studies to date that had directly reported its effect on pain relief in the head and neck patients. Cannon found that transnasal butorphanol appeared to offer a safe alternative to more traditional routes of analgesia delivery in patients undergoing tonsillectomy.\(^{(14)}\) Furthermore, Madani found that transnasal butorphanol with ibuprofen was an effective treatment for moderate-to-severe pain after laser-assisted UPPP and radiofrequency turbinate procedures for severe snoring and chronic nasal congestion.\(^{(15)}\) However, a control group (level 4 evidence) was not clearly discussed in both studies. In this study, we conventionally used oral mefenamic acid and intramuscular meperidine in treating wound pain in the OSA patients after UPPP at the Chang Gung Memorial Hospital (CGMH). The first aim of this study was to further define whether transnasal butorphanol or oral mefenamic acid/intramuscular meperidine was more effective in the treatment of postoperative pain by comparing subjective and objective questionnaires at the 72\(^{th}\) hour following surgery in patients treated in this institution. The second aim was to investigate the safety of two different regimens in a hospital-based study.

**METHODS**

**Subjects**

The study was conducted prospectively in the tertiary referral Sleep Center at the CGMH Linkuo Medical Center. The patients were treated from October 1, 2006 to September 31, 2007. Inclusion criteria of the present study included (1) between the ages of 18-65 years old, (2) body weight between 40-100 kg, (3) having just received the UPPP under general anesthesia and entered this trial within 1 hours after completing surgery, (4) having moderate to severe pain (visual analogue scale $\geq 4$) as result of surgery, (5) on American Society of Anesthesiology (ASA) physical status I or II,\(^{(16)}\) and (6) clear consciousness to answering the questions about his (or her) name, telephone number, and the place where one is (sedation level = 0).

Patients with history of being pregnant women and nursing mothers, who had undergone operations of central neural system, chest and experienced cardiac disease and chronic sinusitis, with higher ASA physical status (> II), on medications such as barbiturate, tranquilizers, antihistamines, and consuming alcohol for more than three consecutive months in the past year, or on concurrent medications such as opioids, analgesics used other than for the surgery or the trial, drugs and/or alcohol abuse, allergy to opioids and hypersensitive to the preservative benzethonium chloride, receiving any other investigational drug within one month preceding randomization, or significant concomitant illness which, in the opinion of the investigator, would interfere with the evaluation of the study medications were excluded from this study.

There were 47 patients with OSA undergoing UPPP during the study period. Because of the limitation of inclusion and exclusion criteria, thirty-one patients obtained were fully explained detail about this study. However, nineteen patients could not pass the consciousness test (sedation level $\geq 1$) and finally...
only 12 patients were enrolled in the present study. Twelve consecutive OSA patients, comprised of 9 men and 3 women with a mean age of 37 ± 9 years, were recruited in this study. All patients had received otolaryngologic examination, including routine oropharyngeal inspection and fiberoptic nasopharyngoscopy on the initial visit. Their mean body mass index (BMI) was calculated as 27.5 ± 5.5 kg/m² and the mean apnea/hypopnea index (AHI) was 37 ± 19 events/hr. After UPPP all patients recovered with clear consciousness and had a mean baseline pain VAS score of 8.3 ± 0.8. Table 1 illustrated the general characteristics of study population in the two pain-treatment groups. The study protocol (serial number: 95-0296b) was submitted and approved by the Institutional Review Board of the Linkou Medical Center of CGMH.

**Polysomnography**

Each patient was examined with at least a standard overnight polysomnography (Nicolet UltraSom System, Madison, WI) in a conventional manner to document sleep parameters and architecture. The AHI was defined as the number of total apnea and hypopnea episodes per hour of sleep. A patient with an AHI ≥ 5 times/hour was diagnosed as an OSA patient.

**Surgical technique**

Key steps of the operation include (1) bilateral tonsillectomy, (2) a box-shape incision of the soft palate, (3) dissection and stripping of the submucosal adipose tissue, (4) developing the uvulopalatal flap, (5) imbricating and suturing the flap to the soft palate, (6) closure of the tonsillar fossa, and (7) maximized lateralization of the posterior pillar.

**Postoperative care**

Intravenous dexamethasone (10 mg) was given immediately before the end of the operation to prevent postoperative airway edema for every patient. Prophylactic antibiotic (ampicillin 500 mg) was given postoperatively every 6 hours for 3 days. During sleep, an oxygen mask with humidity was used to lessen throat discomfort. Vital signs, peripheral arterial oxygen saturation, and adverse events were carefully monitored after operation.

**Pain treatment**

Patients were randomized into two arms to follow different types of pain treatment protocols for postoperative pain relief evaluation. Seven patients in group 1 received transnasal butorphanol (Butaro® Nasal Spray, Lotus Pharmaceutical Co. Ltd, Taipei, Taiwan). They received two nasal sprays of butorphanol (one spray for each nasal cavity, each spray equivalent to 0.1 mL of butorphanol at 10 mg/mL) and another two nasal puffs after one hour if needed, at a 4-hour interval to reduce pain for 3-day hospitalization (maximal daily dose of 12 mg). Meanwhile, the other five patients in group 2 were administered a conventional regimen of mefenamic acid (250 mg, per oral) every 6 hours and intramuscular meperidine (40 mg) every 4 hours pro re nata during hospitalization. No other analgesics were given for both groups in this study.

**Pain assessment**

Postoperative oropharyngeal pain was subjectively measured by a self-assessment visual analogue scale (pain VAS score) that ranged from 0 (no pain) to 10 (extreme pain as you can image). Table 2 demonstrates the clinical global impression of severity (CGI-S score) and improvement (CGI-I score) questionnaires. These two questionnaires not only were applied subjectively by patients to evaluate the severity of and improvement in postoperative pain, and were also were scored by our researchers whom were blinded to the therapeutic regimens. The pain VAS score and CGI-S and CGI-I were assessed at the
Besides, an eight-question self-scoring questionnaire modified from the Patient Diary was also applied to co-evaluate postoperative pain and related morbidities in this study. Table 3 showed this pain-related questionnaire which included four domains of pain severity (overall pain, pain in the throat, difficulty swallowing, and ear pain) as a result of operation and four pain-related morbidities (dysphagia, restriction of physical activity, mouth odor, and disrupted sleep). Patients would rate their level of suffering from each feature using a four-point Likert-type scale (ratings of 0–3 indicated no pain to severe pain) at the 72th hour after surgery. Moreover, each patient was asked the severity of bodily pain in the past 72 hours postoperative period by a self-assessment questionnaire that was modified from the 36-item short form of quality of life (SF-36 bodily pain). Patients used a six-point Likert-type scale from 1 (no pain) to 6 (very severe pain) to rate their bodily pain.

### Statistical analysis

Statistical analysis was performed using the independent Mann–Whitney U test to compare the gender, age, BMI, AHI, pain VAS score, CGI-S, CGI-I, scores of pain and pain-related morbidities, SF-36 bodily pain, and adverse events between the two groups. The Wilcoxon signed rank test was used to compare baseline and 72 hours postoperatively pain VAS score, CGI-S, and CGI-I in both groups. The Spearman rank-order correlation coefficient was used to compare the satisfaction scores and pain-related symptom scores. Statistical analyses were performed using SPSS 11.0 for Windows (SPSS Inc., Chicago, IL). Results were expressed as mean ± standard deviation (SD). A two tailed p value of less than 0.05 was considered significant.

### RESULTS

#### Patients

All twelve patients completed the scheduled assessments during hospitalization. Patients’ characteristics of the two pain-treatment groups were shown in Table 1. The distributions of the gender, age, AHI, and baseline-pain score were similar (p > 0.05). However, the mean BMI of the group 1 was significantly smaller than that of the group 2.
(p = 0.03) due to a particular obese woman (BMI = 38.5 kg/m²) in the group 2 patients. Nevertheless, her bodyweight of 91.3 kg fitted in the inclusion criteria.

**Adverse effects**

None of the studied patients developed postoperative bleeding. Three patients had moderate nausea and vomiting after taking medications taken (one in group 1 [14%] and two in group 2 [40%], p = 0.33). No serious adverse effects, such as sedation, respiratory distress, airway compromise, cardiac arrhythmia, or pulmonary edema, were noted in either group. Therefore, there was no difference in the occurrence of postoperative major complications between Groups 1 and 2.

**Mean rating in pain VAS and CGI-S and CGI-I scores**

Due to the small number of subjects in each group and the small amount of change from pre- to posttreatment in some categories, statistical significance (p < 0.05) was not obtained in all categories.

A graph of changes of the pain VAS scores after UPPP in two groups was presented in Fig. 1. The mean pain VAS score for the group 1 significantly reduced from 8.6 ± 0.8 (1 h) to 3.4 ± 0.8 (72 h) (p = 0.02), and that of the group 2 was also significantly reduced from 8.0 ± 0.7 (1 h) to 2.0 ± 1.0 (72 h) (p = 0.04). When comparing the decreased VAS scores between these two groups, no statistical significance was obtained (p = 0.41).

Fig. 2 demonstrated the averaged CGI-S scores in both the treatment groups. The mean CGI-S scores of the butorphanol group significantly improved from 4.7 ± 0.5 (1 h) to 2.7 ± 0.8 (72 h) (p = 0.03). A trend toward improvement in CGI-S scores in group 2 was found (4.4 ± 1.3 to 2.8 ± 0.8, p = 0.10). However, the change of CGI-S scores between two groups showed no statistical significance as the p value as calculated to be 0.86.

When assessing the improvement of illness by CGI-I scores, group 1 patients showed notable improvement from 3.3 ± 0.5 (1 h) to 2.3 ± 0.5 (72 h) (p = 0.02) and group 2 patients also tended to improve from 3.6 ± 0.9 (1 h) to 2.2 ± 0.8 (72 h) (p = 0.06). The changes in CGI-I again showed no statistical difference between both groups (p = 0.52).

**Mean rating in pain and related symptoms and SF-36 bodily pain**

Pain and related morbidities were evaluated at the 72th hour following surgery. No significant difference was noted in all domains of pain and related morbidities between two groups (Table 4). Additionally, the difference of SF-36 bodily pain in the 72th hour postoperatively between both groups did not reach statistical significance (4.3 ± 1.0 vs. 3.4 ± 1.5, p = 0.32).

![Fig. 1](image) Evaluation of perceptual change of pain visual analogue scale (VAS) scores from treatment. When comparing pre- and post-treatment scores within the two groups, pain VAS score obtained statistical significance (p < 0.05) in both treatment groups. When comparing the decreased pain VAS scores between the treatment groups (arrow A vs. arrow B), statistical significance was not obtained (p = 0.41), indicating that the similar efficacy in pain reduction between two treatment regimen.
Correlation of SF-36 bodily pain, pain VAS, CGI-S, CGI-I, and pain and related syndrome scores

SF-36 bodily pain was significantly correlated to VAS ($r = 0.68$, $p = 0.02$), CGI-S ($r = 0.60$, $p = 0.04$), CGI-I ($r = 0.59$, $p = 0.04$), overall pain ($r = 0.87$, $p < 0.001$), throat pain ($r = 0.66$, $p = 0.02$), and throat pain during swallowing ($r = 0.61$, $p = 0.04$). Otherwise, it was insignificantly correlated with ear pain, dysphagia, restriction of physical activity, mouth odor, and disrupted sleep ($r = 0.38$, $0.55$, $-0.05$, $0.04$, & $0.53$, respectively; all $p > 0.05$, data not shown).

DISCUSSION

Our investigation had weaknesses inherent in this type of prospective randomized study. Only twelve patients enrolled and completed the study and a computer program-assisted randomization resulted in two heterogeneous groups with unequal case numbers and an uneven distribution of BMI. Moreover, this study would have been better to have both groups treated with opioid analgesics via same route for result comparison. However, our previous study showed that difference in route of administration
may result in different outcomes in lessening postoperative pain.\(^3\)

In our study population, transnasal butorphanol and oral mefenamic acid/intramuscular meperidine demonstrated similar improvement efficacies in the three pain outcomes (pain VAS and CGI-S and CGI-I scores) and comparable final results in the eight-item pain and related morbidities and SF-36 bodily pain measured. Besides, both regimens produced tantamount adverse effects. In fact, the differences in amount of pre- to posttreatment change and occurrence of adverse events between the two groups were too small to demonstrate that one treatment modality was more effective or safer than the other with the 12 patients presented herein. This suggested that in our heterogeneous OSA treatment groups, transnasal butorphanol and oral mefenamic acid/intramuscular meperidine yielded equivalent pain improvement at three days posttreatment.

Each studied subject underwent UPPP included tonsillectomy and partial resection of the soft palate and uvula and experienced considerable postoperative pain (pain VAS score = 8.3 ± 0.8). Previous studies indicated most patients undergoing UPPP had high pain scores during the first 24 postoperative hours.\(^3,20\) In this study, patients who received transnasal butorphanol treatment experienced severe-worst postoperative pain (pain VAS score = 8.6 ± 0.8) at the initial interview (1 h) and mild-moderate pain since the 12th to the 72th hour (pain VAS score: 12 h = 4.0 ± 2.6; 24 h = 3.9 ± 1.5; 72 h = 3.4 ± 0.8). Our data indicated that transnasal butorphanol produced considerable pain relief for OSA patients after UPPP within the first 12 postoperative hours, and continued to alleviate pain gradually and subsequently, whereas the group 2 patients also had severe-worst pain (pain VAS score = 8.0 ± 0.7) at the initial interview, moderate pain (pain VAS score = 6.0 ± 1.7) at the 12th hour, mild-moderate (pain VAS score = 3.2 ± 1.6) at the 24th hour, and mild (pain VAS score = 2.0 ± 1.0) postoperative pain at the 72th hour. Accordingly, our results supported the use of intranasal butorphanol as a pain relief earlier than the oral mefenamic acid/intramuscular meperidine regimen.

A multidimensional approach was indicated to assess the quality of care. In this study, we used three questionnaires to investigate postoperative pain: pain VAS score self-reported by patients and CGI-S/CGI-I scores evaluated by the doctors. CGI questionnaires are popularly applied to assess the psychological severity and improvement by professionals in depression and schizophrenia.\(^19\) To our knowledge, this study was the first report to administer the CGI-S/CGI-I scores to rate the severity and improvement of postoperative oropharyngeal pain. A clear trend showed that intranasal butorphanol could quickly reduce postoperative pain within 12 hours and oral mefenamic acid/intramuscular meperidine could effectively alleviate pain during a period of 12 to 24 hours posttreatment (Fig. 1 & Fig. 2). Objective improvement of postoperative pain was obtained gradually after pain treatment, with the exception that group 2 patients were not improved by medications at the 12th postoperative hour as illustrated in Fig. 3. This finding might suggest that oral mefenamic acid/intramuscular meperidine exhibited a poor anesthetic effect during night sleep.

At the end of the hospital-based observation, two additional self-reporting questionnaires were obtained in order to evaluate eight dimensions of postoperative pain and bodily pain in quality of life commonly experienced postoperatively. Our data showed that both groups had parallel levels of pain and related morbidities (Table 4) and SF-36 bodily pain.

In the present study, the SF-36 bodily pain score represented an entire pain evaluation during the 72 hours of hospitalization after operation. Although the length of hospital stay was far from the standard stay in the U.S. (day surgery), we had a better chance to well inspect the recovery of postoperative pain and associated morbidities of both regimens in such a study. Accordingly, this substantial investigation on quality of life demonstrated that patients experienced moderate pain (mean SF-36 bodily pain score = 3.9 ± 1.2) after UPPP despite of anesthetic agents usage. In decreasing order, SF-36 bodily pain was correlated well with overall pain, pain VAS, throat pain, throat pain during swallowing, CGI-S, and CGI-I. These relationships revealed that pain VAS, CGI-S, and CGI-I questionnaires were valid tools to measure the level of postoperative pain. Besides, reductions of overall pain, throat pain, and throat pain during swallowing were the keystones of the pain treatment.

In conclusion, this investigation confirmed the efficacy of transnasal butorphanol and oral mefe-
namic acid/intramuscular meperidine in the treatment of postoperative pain among OSA patients undergoing UPPP. The rapid pain alleviation achieved without an oral administration or supplementary injection may also offer the benefits of improved oropharyngeal pain and related morbidities in transnasal butorphanol-treated patients. This study also confirmed the safety of transnasal butorphanol in patients undergoing oropharyngeal surgery.

Acknowledgements
The authors are grateful for the grants from Lotus Pharmaceutical Co. Ltd, Taipei, Taiwan (BUTA-CGMH-LK-01) and Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan, Taiwan (XMRPG-350611). The grant source had no role in designing or implementing the study or deciding to select study individuals.

REFERENCES
11. Joyce TH III, Kubicek MF, Skjonsby BS, Jones MM.


經鼻 butorphanol 噴劑對於懸垂型頸咽手術前後疼痛控制——一個以住院為主的隨機分組研究

黃皓駿 李立昂 方瑞仁 李學禹 羅景家 吳若瑄

背 景：經鼻止痛噴劑是一種控制手術後疼痛的新方法。在本研究中，我們評估經鼻 butorphanol 噴劑對於阻塞性睡眠呼吸中止症病人經懸垂型頸咽手術後其疼痛控制的功能，並與口服 mefenamic acid 併肌肉內注射 meperidine 相比較於疼痛減輕的效果。

方 法：這個前瞻性、隨機分組，公開標示的研究是由一個三級照護的睡眠中心所執行。本研究納入 12 位阻塞性睡眠呼吸中止症病人於接受懸垂型頸咽手術後，有完整的意識且仍至少遭受顯著以上的口咽疼痛（疼痛分數大於或等於 4 分）。這些病人被隨機分組接受經鼻 butorphanol 噴劑（樣本個數為 7）或口服 mefenamic acid 併肌肉內注射 meperidine（樣本個數為 5）。於術後第 12、24 及 72 小時以疼痛視覺量表 (pain visual analogue scale, VAS) 與臨床整體嚴重度印象 (Clinical Global Impression in Severity, CGI-S) 與臨床整體改善印象 (Clinical Global Impression in Improvement, CGI-I) 來評估口咽疼痛。我們亦於術後第 72 小時評估術後疼痛相關併發症 (postoperative pain related morbidities, PRMs) 與身體疼痛之生活品質 (quality of life in bodily pain, QOL-BP)。我們在病患住院的時間內仔細的監控任何有關疼痛治療所衍生的不良事件。

結 果：整個研究中並無發生重大的併發症。在分析經鼻 butorphanol 噴劑組的臨床測量時，我們發現不論是 VAS (p = 0.04)，CGI-S (p = 0.03)，和 CGI-I (p = 0.02) 均有顯著地改善。然而，若與口服 mefenamic acid 併肌肉內注射 meperidine 比較疼痛減輕的程度時，之前所提之三項變數與 PRMs 和 QOL-BP 均無顯著之差別。

結 論：於阻塞性睡眠呼吸中止症病人，使用經鼻 butorphanol 噴劑可以顯著的減輕因懸垂型頸咽手術所產生的術後疼痛。本研究亦證實在受術口咽手術的病人使用經鼻 butorphanol 噴劑之安全性。

(長庚醫誌 2009;32:390-9)

關鍵詞：butorphanol，減輕疼痛，阻塞性睡眠呼吸中止症，懸垂型頸咽手術，術後疼痛