Sublingual Buprenorphine Versus Intramuscular Meperidine in Post-Operative Pain Relief

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== 국문초록 ==

鹽酸 Buprenorphine의 舌下投與에 의한 下腹部手術後의 鎮痛效果

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鹽酸 buprenorphine은 1966年 英國의 Reckitt와 Colman社에서 合成된 拮抗性 鎮痛劑로서, morphine보다 더 複雜한 化學構造를 갖으며, 그 鎮痛効力이 他 鎮痛劑보다 比較的 強하고 長時間 持續된다는 特性이 있어 術後 鎮痛 目的으로도 使用되고 있다.

本 延世醫院 麻酔科學 教室에서는 1986年 12월부터 4월까지 美國麻酔科學會 患者分類 1내지 2에 屬하는 30~60歲 女子患者中 全身麻酔下에 腹式子宮切除術을 받은 60名의 患者를 對象으로 하여 이중 30名을 無作爲 抽出하여, 鎮痛을 呼訴할 때마다 注射用 buprenorphine 0.3 mg을 舌下投與하였다(SL-buprenorphine群). 手術後 病室에서 鎮痛 目的으로 meperidine을 筋注한 30名을 對照群(IM-meperidine群)으로 하여, 鹽酸 buprenorphine의 鎮痛持續期間, 投與回數 및 投與後 副作用 등을 對照群과 比較觀察, 舌下投與된 鹽酸 buprenorphine의 鎮痛效果에 대한 다음의 結論을 얻은바 文獻의 考察과 함께 報告하는 바이다.

1) SL-buprenorphine群에서 平均 鎮痛持續期間은 18.27 ± 4.98 時間으로서 IM-meperidine群에서의 鎮痛持續時間 5.71 ± 2.49 時間보다 的의 있게 길었다($p < 0.001$).

2) 手術後 24時間以內에 投與된 鎮痛劑의 總量은 각각 SL-buprenorphine群이 $8.49 \pm 3.48 \mu\text{g} \cdot \text{kg}^{-1}$ 이었고 IM-meperidine群이 $3.05 \pm 1.20 \text{mg} \cdot \text{kg}^{-1}$ 이었다.

3) 手術後 鎮痛劑 投與回數는 SL-buprenorphine群에서 平均 1.57 ± 0.63 回로서 IM-meperidine群의 3.5 ± 1.28 회보다 현저히 적은 投與回數를 나타내었다($p < 0.05$).

4) SL-buprenorphine群에서의 動脈血 gas分析結果는 手術前과 投與後에 有意한 差異가 없다.

5) 兩群에서 注目되는 副作用으로서는 惡心, 嘔吐, 睡眠狀態, 眩氣症 등이 있었으나 그 程度는 重하지 않았다.

이상에서 舌下投與되는 buprenorphine을 臨床適用한 結果, buprenorphine은 安全하고 長時間持續性이며, 比較的 強力한 鎮痛劑로서 投與가 容易한 점을 觀察하였기에 手術後오는 鎮痛治療에 有效하다는 結論을 얻었다.

Key Words: Sublingual buprenorphine, Postoperative pain relief

Pain relief after surgery is not always satisfactory in the ward. A majority of patients complained of severe pain after lower abdominal surgery as a result of delays in drug administration or other factors such as the intermittent nature of drug

administration, and variability in the rate of absorption¹⁾.

A regular dosing regimen is less adaptable to patient needs and the management of postoperative pain. One means of providing better relief is by using

a "patient demand" analgesia system²¹). It seems that higher doses are required when the drugs are administered regularly rather than on patient demand.

The relatively new synthetic opiate analgesic buprenorphine can serve to obviate these problems. On demand sublingual buprenorphine has great advantages in its ability to provide effective analgesia over a long period of action, with ease of administration, and mild degree side effects^{1,3,4}).

The aim of this study was to evaluate the efficiency, side effects and feasibility of sublingual buprenorphine as compared to intramuscular meperidine for relief of postoperative pain.

METHODS

1) Patient selection

The trial was conducted on sixty female patients aged 30~60 yrs who were undergoing an elective transabdominal hysterectomy involving lower abdominal incision under general anesthesia. Any patient suffering from a known cardiovascular, hepatic, renal, or endocrine disorder was excluded. The patients were divided into two groups at random a SL-buprenorphine group and an IM-meperidine group.

2) Anesthetic technique

Before surgery, the patients were premedicated with hydroxyzine $1\text{mg}\cdot\text{kg}^{-1}$ and glycopyrrolate $4\text{ug}\cdot\text{kg}^{-1}$ intramuscularly after informed consent was obtained. Anesthesia was induced with thiopental $5\text{mg}\cdot\text{kg}^{-1}$ (2.5 %) and suxamethonium $1\text{mg}\cdot\text{kg}^{-1}$ intravenously. After endotracheal intubation, anesthesia was maintained with halothane 1~2% or enflurane 1~1.5% and nitrous oxide 50% in oxygen. No parenteral analgesics were given during surgery and the anesthetic technique was standardized in all patients. Muscle relaxation was obtained by pancuronium $0.08\text{mg}\cdot\text{kg}^{-1}$ intravenously. At the end

of surgery, the anesthetic gases were discontinued and residual neuromuscular blockade was antagonized with atropine 1.0 mg and neostigmine 2.0 mg i. v. The patients were extubated, transferred to the recovery room, and remained there until consciousness had returned.

3) Drug administration

SL-buprenorphine group:

Immediately after transfer to the recovery room, oxygen was given by nasal cannula for a while. When the patient became conscious, cooperative, and irritable due to pain, the oxygen cannula was removed and buprenorphine (0.3 mg ampule) was administered sublingually. When further analgesia was required, subsequent doses of buprenorphine were given on demand in the ward during the first 24 postoperative hours.

IM-meperidine group:

For postoperative pain relief, IM. meperidine 50 mg was given at regular intervals as demanded. This was done by the conventional method in which during the immediate postoperative period, all the patients in this group were given a first single dose of IM. meperidine. But after that, IM meperidine was permitted to be given at four hours interval only when there was a subsequent requirement.

4) Observation and study

The observer waited until the patient became awake and cooperative after transfer to the recovery room. In each group upon complaint of pain, a single dose of analgesic was administered. Immediately after administration of the analgesic drugs with each pain assessment, measurements of vital signs, degree of respiratory depression, sedation, and possible side effects were conducted by a single observer for two to three hours in the recovery room. In the SL-buprenorphine group, arterial blood was sampled twice for blood gas analysis, before the operation and one hour after buprenorphine adminis-

tration. Each patient was asked about the degree of pain experienced and the level of pain relief.

After each patient became stable, she was transferred to the ward and observed by trained nurses. Observers made records of vital signs and side effects upon each subsequent analgesic administration in the ward. Twenty four hours after surgery, all the patients were interviewed in order to record any unnoticed symptoms and to evaluate analgesic effects.

The duration of analgesic effect was measured from the the time of previous analgesic administration to the subsequent administration. Total requirements of analgesics in each group during the first 24 postoperative hours were assessed. The number of analgesics administered in the two groups were compared nonparamedically between treatments, using the Mann-Whitney rank sum test where appropriate.

RESULTS

Of the 67 patients who entered the study, 60 completed the trial. Data from seven patients were ex-

cluded because sublingual buprenorphine was swallowed. Thirty patients received SL-buprenorphine and thirty received IM-meperidine.

The demographic data for the patients are shown

Table 1. Patient Data

	SL-Buprenorphine (n = 30)	IM-Meperidine (n = 30)
Age (yr)	42.67 ± 6.90	42.40 ± 6.67
Body weight (kg)	55.85 ± 5.62	58.21 ± 5.93
Duration of surgery (hr)	2.93 ± 0.85	2.78 ± 0.95

Table 2. The Duration of Pain Relief and its Ratio between SL-buprenorphine and IM-meperidine Groups

	SL-Buprenorphine (n=30)	IM-meperidine (n = 30)
Duration of pain relief		
Range (hr)	4.42 — 24.00	1.17— 13.00
Mean ± SD (hr.)	18.27 ± 2.98*	5.17 ± 2.49
Ratio of duration of pain relief between the two groups	3.2 : 1.0	

* : p < 0.001

Fig. 1. Number of analgesic dosages required during the first postoperative 24 hours, SL-buprenorphine group (hatched bar), IM-meperidine group (clear bar)

Table 3. Total Dosage of Analgesic during the First Postoperative 24 Hours

Total dose	SL-Buprenorphine ($\mu\text{g. kg}^{-1}$) (n = 30)	IM-meperidine (mg. kg^{-1}) (n = 30)
Range	4.48–11.74	1.47–3.85
Mean $\pm$ SD	8.49 $\pm$ 3.48	3.05 $\pm$ 1.20

in Table 1. Age, weight, and duration of surgery were not found to have statistically significant differences between the two groups (Table 1). The duration of analgesic effect shows a wide range of variation (Table 2). The mean duration of the analgesic effect was significantly longer in the SL-buprenorphine group ($p < 0.001$). Some patients in the SL-buprenorphine group did not require additional analgesia after the first dose.

Table 2 shows that the mean duration of the analgesic effect was 3.2 times longer in the SL-buprenorphine group than in the IM-meperidine group. There is a statistically significant difference between the two groups ($p < 0.05$) in the number of analgesic doses administered. The additional requirement for analgesics in the SL-buprenorphine group was less than in the IM-meperidine group (Fig. 1).

The total analgesic dosage requirements during the first postoperative 24 hours are shown in Table 3. In the SL-Buprenorphine group, there were minimal changes in arterial blood gas values between preoperative and postoperative states after sublingual buprenorphine administration (Table 4). All postoperative values were within normal limits and no respiratory acidosis occurred.

Fig. 2 shows the incidence of side effects after each analgesic administration. Nausea and vomiting were more common in the IM-meperidine group and a sleepy state and dizziness were more common in the SL-buprenorphine group. The incidence of Nausea and vomiting was high early the next morning. Continuous nausea is the major side effect after

Table 4. Arterial Blood Gas Values in the SL-Buprenorphine Group (n = 26)

	Preoperative state (Mean $\pm$ SD)	1 hr after SL-buprenorphine (Mean $\pm$ SD)
PaO ₂ (torr)	100.84 $\pm$ 17.58	96.27 $\pm$ 19.34
PaCO ₂ (torr)	35.13 $\pm$ 4.34	35.19 $\pm$ 5.73
pH	7.45 $\pm$ 0.02	7.43 $\pm$ 0.03
BE (mEq/L)	2.45 $\pm$ 0.81	1.26 $\pm$ 7.34

Fig. 2. Side effects after SL-buprenorphine (hatched bar) and IM-meperidine (clear bar) administration.

opioid administration, but the incidence was higher in the IM-meperidine group. Severe vomiting was reported in one patient of the SL-buprenorphine group and a sleepy state was more common than in the IM-meperidine group. However, we observed that the patients who were treated with sublingual

Fig. 3. Structural formulae.

Table 5. Standard Doses of Oral Analgesics Expressed as Equi-analgesic Doses of intramuscular Morphine (Adapted from Houde 1979)

Drug	Standard p.o. dose (mg)	Approximate equivalent dose of 1 M morphine (mg)
Pethidine	100	3
Pentazocine	50	3
Dextropropoxyphene	65	3
Dilhydrocodeine	30 ⁺	3
Buprenorphine (sublingal)	0.2	3–3.6*

⁺ From Data Compendium, Duncan, Flockhart & Co. Ltd, DF 118

* Wallenstein et al (1981)

buprenorphine were more comfortable throughout the postoperative period.

DISCUSSION

Buprenorphine, N-cyclopropylmethyl-7-(1S-hydroxy, 1,2,2, trimethylpropyl)-6, 14-endoethano-6, 7,8,14-tetrahydronororipavine hydrochloride, is a recently developed agent derived from the opium

Fig. 4. Structural diagrams of buprenorphine and diprenorphine.

alkaloid thebaine. It was synthesized in 1966 in the laboratories of Reckitt and Colman in Britain and has been studied widely in both animals and man. The interest in this drug stems from its mixed properties of powerful agonist and antagonist action. As an agonist, the chemical structure is very similar to morphine (Fig. 3), but it achieves such a high opiate receptor occupancy that it provides a 25 to 40 times more potent analgesic effect than morphine after parenteral injection⁷⁾. Previous studies comparing sublingual buprenorphine with intramuscular morphine have used ratios of 0.6: 15 mg (1:25)¹⁴⁾, 0.3: 12.5 mg (1:42) and 0.4: 10 mg (1:25)^{1,3,9)}. Kamel compared i.v. buprenorphine with i.v. meperidine at ratios of 5.0 μgkg^{-1} : 1.0 mg $\cdot$ kg⁻¹ (1:200)¹²⁾. In the light of Houde and Wallenstein's equipotency ratios (Table 5)²⁷⁾, the dosages of meperidine used in our study appear relatively small when compared with the dosages of sublingual buprenorphine—5.0 μgkg^{-1} : 0.83 mg $\cdot$ kg⁻¹ (1:166). However, the total dosages of meperidine given during the first postoperative 24 hours are rather larger than that of sublingual buprenorphine—8.49 μgkg^{-1} : 3.05 mgkg⁻¹ (1:359) (Table 3). This is due to the intramuscular meperidine being given more frequently than the sublingual buprenor-

phine during the first postoperative 24 hours (Fig. 1). Buprenorphine is also a narcotic antagonist. Figure 4 also shows buprenorphine and its closely related structure diprenorphine, a potent narcotic antagonist. It contains a cyclopropylmethyl substitution similar to that in the narcotic antagonists cycloazocine and naltrexone²²). Cowan demonstrated that buprenorphine antagonizes the antinociceptive actions of morphine in the mouse and rat tail flick test⁷). It is approximately 3 times stronger, with a duration of action 6 times longer, than naloxone⁸). Jasinski showed that very large doses (8 mg) are capable of blocking the effect of large doses of morphine (up to 120 mg) for more than 30 hours⁶).

A major interest underlying this study was the unusually long action duration of buprenorphine. In 1976, Hambrook and Rance's research showed unusual receptor kinetics of buprenorphine⁸). In an early unpublished study in man, the elimination half-life of labelled buprenorphine appears to be more than 12 hours and possibly more than 24 hours²⁴). Furthermore, its slow dissociation constant of the drug receptor complex permits a prolonged drug effect in the presence of low plasma concentration²⁹). This has been proved clinically by many published studies¹⁻²⁰). This present study also shows the significantly longer duration ($p < 0.001$) of analgesia in the SL-buprenorphine group than that in the IM-meperidine group (Table 2).

Another merit of this drug is its high lipophilicity. It is known that buprenorphine and methadone are the most lipophilic analgesics and are readily absorbed through sublingual administration²⁵). Pharmacokinetic study shows that systemic availability by this route is 58% for a 0.4 mg dose (range 44-78%)²⁰). Previous studies assessed the analgesic effect of this drug with various applied routes: I.V.¹²), I.M.¹³), epidural¹¹), caudal²⁶), and sublingual^{1-3,4,9,10,11,16,20}). In spite of the variable administrative routes, their conclusions concided with buprenorphine's achievement of better analgesia and longer duration of

action over comparable analgesic regimens.

Despite its potency and longer duration of action, buprenorphine appears to have weak respiratory depressant activity. It is now known that respiratory depression may occur, but the effects are not directly dose-related¹³). Measurement of its respiratory effect has been performed by many previous authors^{9,15,20,24}). Their observations, including respiratory parameters, show various degrees of diminution in respiratory rate^{9,20,24}), FVC, PEV₁ and peak flow below preoperative values¹⁵). McQuay et al show blood gas results. They observed increased PaCO₂ values after surgery, but paCO₂ did not increase following the second dose of buprenorphine²⁸). Cuschieric et al found significant hypoxemia and greater carbon dioxide retention following drug administration⁹). But all of their results do not seem to be supported as the sole effect of sublingual buprenorphine since there are many other factors, such as sampling time and residual anesthesia, which could alter the blood gas results. Furthermore, these respiratory depressant effects were not more serious than those of other established analgesics^{9,13,28}) except in Cook's study²⁴).

Our study shows no remarkable difference in PaCO₂ and PaO₂ from preoperative values (Table 4). In observing the respiratory effect of sublingual buprenorphine sampling, time is important, according to Bullingham's research which shows that satisfactory analgesia was achieved 0.5 hours after sublingual buprenorphine and peak plasma concentration of the drug occurred 3 hours after administration²³). We designed our study to sample blood for gas analysis at 1 hour after the first dose of buprenorphine instead of 3 hours, which would have been the optimum time to sample the blood for the peak plasma concentration of the drug.

Single doses of buprenorphine 0.3 mg did not cause any fall in blood pressure in this study. Hayes et al found no adverse hemodynamic effects following intravenous buprenorphine 0.3 mg¹⁸) and this result

parallels our observation.

Throughout the period of study, to assess the value of sublingual buprenorphine, possible side effects were observed. Our results are comparable to other studies. Previous studies have reported varied frequencies of side effects¹⁻²⁰. A sleepy state was the most common side effect observed in the SL-buprenorphine group (Fig. 2). Some patients fell into a deeper drowsy state and significantly more sedation was produced in the SL-buprenorphine group than in the IM-meperidine group, but the difference was not clinically important. This result supports previous observations^{1,13,15}. Our record shows only two cases of dizziness in the SL-buprenorphine group. Edge observed that dizziness increased significantly with higher dose levels of buprenorphine⁹. In our study, the incidence of nausea and vomiting was higher in the IM-meperidine group than in the SL-buprenorphine group (Fig. 2) and this incidence is a little higher than in other previous studies^{11,13,19} but not in Carl's study¹⁵.

While researchers have their favored methods to evaluate and express the analgesic effect of an agent, there is a potential for great inaccuracy and inconsistency stemming from patient subjectivity. Despite the objectivity of a trained observer, some patients will exaggerate the severity of their pain, and some will not. For this reason, this study did not adopt the pain scoring method. Rather, we observed the duration of analgesia, and the frequency of drug requirement.

This study employed 50 mg of injectable meperidine in an intramuscular route for the control group since it is the standard analgesic regimen given in our gynecology ward after surgery. For the other group, we adopted 0.3 mg of injectable buprenorphine in a sublingual route. However, 0.4 mg sublingual buprenorphine tablet (Temesic®, Reckitt and Colman plc), which was available for Derbyshire's study², could be considered.

These observation needs further confirmation, but

the object of this study was to explore the superiority of sublingual buprenorphine in pain relief. The results of this study indicate that sublingual buprenorphine 0.3 mg provides significantly better pain relief sustained over 18.27 ± 4.98 (Mean $\pm$ SD) hours and has the advantage of easy administration over intramuscular meperidine 50 mg. There were no serious side effects or significant differences in incidence between the two groups other than sedation.

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