Sublingual Buprenorphine Versus Intramuscular Meperidine in Post-Operative Pain Relief

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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 absorption. 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 system\textsuperscript{11}. 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\textsuperscript{3,4,5}.

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 1mg·kg\textsuperscript{-1} and glycopyrrolate 4 ug·kg\textsuperscript{-1} intramuscularly after informed consent was obtained. Anesthesia was induced with thiopental 5 mg·kg\textsuperscript{-1}(2.5 %) and suxamethonium 1 mg·kg\textsuperscript{-1} intravenously. After endotracheal intubation, anesthesia was maintained with halothane 1–2% or enfurane 1–1.5% and nitrousoxide 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 mg·kg\textsuperscript{-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 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 excluded because sublingual buprenorphine was swallowed. Thirty patients received SL-buprenorphine and thirty received IM-meperidine.

The demographic data for the patients are shown

<table>
<thead>
<tr>
<th>Table 1. Patient Data</th>
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<tr>
<td>Age (yr)</td>
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<tr>
<td>Body weight (kg)</td>
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<td>Duration of surgery (hr)</td>
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<tr>
<th>Table 2. The Duration of Pain Relief and its Ratio between SL-buprenorphine and IM-meperidine Groups</th>
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<tbody>
<tr>
<td>SL-Buprenorphine (n=30)</td>
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<tr>
<td>Duration of pain relief</td>
</tr>
<tr>
<td>Range (hr)</td>
</tr>
<tr>
<td>Mean ± SD (hr.)</td>
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<tr>
<td>Ratio of duration of pain relief between the two groups</td>
</tr>
</tbody>
</table>

* : 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

<table>
<thead>
<tr>
<th>Total dose</th>
<th>SL-Buprenorphine (ug. · kg⁻¹) (n = 30)</th>
<th>IM-meperidine (mg. · kg⁻¹) (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>4.48 - 11.74</td>
<td>1.47 - 3.85</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>8.49 ± 3.48</td>
<td>3.05 ± 1.20</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Standard p.o. dose (mg)</th>
<th>Approximate equivalent dose of 1 M morphine (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pethidine</td>
<td>100</td>
<td>3</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>Dextropropoxyphene</td>
<td>65</td>
<td>3</td>
</tr>
<tr>
<td>Dilhydrocodeine</td>
<td>30†</td>
<td>3</td>
</tr>
<tr>
<td>Buprenorphine (sublingual)</td>
<td>0.2</td>
<td>3–3.6*</td>
</tr>
</tbody>
</table>

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

buprenorphine were more comfortable throughout the postoperative period.

**DISCUSSION**

Buprenorphine, N-cyclopropylmethyl-7-(1-S-hydroxy, 1,2,2, trimethylpropyl)-6, 14-endethano-6, 7,8,14-tetrahydronororipavine hydrochloride, is a recently developed agent derived from the opium 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 injection\(^7\). Previous studies comparing sublingual buprenorphine with intramuscular morphine have used ratios of 0.6: 15 mg (1:25)\(^4\), 0.3: 12.5 mg (1:42) and 0.4: 10 mg (1:25)\(^1\,3\,8\,9\). Kamel compared i.v. buprenorphine with i.v. meperidine at ratios of 5.0 \(\mu gkg^{-1}\): 1.0 mg · kg\(^{-1}\) (1:200)\(^1\,2\). In the light of Houdé and Wallenstein's equipotency ratios (Table 5)\(^2\,7\), the dosages of meperidine used in our study appear relatively small when compared with the dosages of sublingual buprenorphine — 5.0 \(\mu gkg^{-1}\): 0.83 mg · 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 \(\mu gkg^{-1}\): 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 cyclazocine and naltrexone\textsuperscript{22}. Cowan demonstrated that buprenorphine antagonizes the antinociceptive actions of morphine in the mouse and rat tail flick test\textsuperscript{7}. It is approximately 3 times stronger, with a duration of action 6 times longer, than naloxone\textsuperscript{6}. 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 hours\textsuperscript{8}.

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 buprenorphine\textsuperscript{9}. 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 hours\textsuperscript{24}. Furthermore, its slow dissociation constant of the drug receptor complex permits a prolonged drug effect in the presence of low plasma concentration\textsuperscript{29}. This has been proved clinically by many published studies\textsuperscript{1~20}. 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 administration\textsuperscript{40}. Pharmacokinetic study shows that systemic availability by this route is 58% for a 0.4 mg dose (range 44~78 %)\textsuperscript{29}. Previous studies assessed the analgesic effect of this drug with various applied routes: I.V.\textsuperscript{12}, I.M.\textsuperscript{13}, epidural\textsuperscript{119}, caudal\textsuperscript{10}, and sublingual\textsuperscript{1~3,4,8,10,11,15,20}. In spite of the variable administrative routes, their conclusions coincided 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-related\textsuperscript{18}. Measurement of its respiratory effect has been performed by many previous authors\textsuperscript{8,15,20,24}. Their observations, including respiratory parameters, show various degrees of diminution in respiratory rate\textsuperscript{8,20,24}, FVC, PEV, and peak flow below preoperative values\textsuperscript{15}. McQuay et al. show blood gas results. They observed increased PaCO$_2$ values after surgery, but PaCO$_2$ did not increase following the second dose of buprenorphine\textsuperscript{28}. Cuscherie et al. found significant hypoxemia and greater carbon dioxide retention following drug administration\textsuperscript{49}. 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\textsuperscript{9,12,28} except in Cook's study\textsuperscript{24}.

Our study shows no remarkable difference in PaCO$_2$ and PaO$_2$ 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 administration\textsuperscript{29}. 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 mg\textsuperscript{18} 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 effects\(^1\)\(^{19}\). A sleepy state was the most common side effect observed in the SL-buprenorphin 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\(^1\)^\(^{13}\)\(^{19}\). Our record shows only two cases of dizziness in the SL-buprenorphine group. Edge observed that dizziness increased significantly with higher dose levels of buprenorphine\(^1\). 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\(^1\)^\(^{13}\)\(^{19}\) but not in Carl’s study\(^1\)\(^{13}\).

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\(^6\), Reckitt and Colman plc), which was available for Derbyshire’s study\(^7\), 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 ± 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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