Effects of Intravenous Patient-Controlled Analgesia With Buprenorphine and Morphine Alone and in Combination During the First 12 Postoperative Hours: A Randomized, Double-Blind, Four-Arm Trial in Adults Undergoing Abdominal Surgery

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ABSTRACT

Background: Intense pain in the first 12 hours after major abdominal surgery requires the use of large amounts of analgesics, mainly opioids, which may produce undesirable effects. Buprenorphine (BUP) is not typically used intravenously in this setting, particularly in combination with morphine (MO), due to concerns that BUP might inhibit the analgesic effect of MO.

Objective: This study compared the analgesic effect of BUP and MO separately and in combination for postoperative pain control in patients undergoing abdominal surgery.

Methods: In this double-blind study, adult patients were randomized to receive 1 of 4 regimens for 12 hours: a basal BUP infusion (BUP-i) of 0.4 μg/kg/h + BUP boluses (BUP-b) of 0.15 μg/kg each; a basal MO infusion (MO-i) of 10 μg/kg/h + MO boluses (MO-b) of 5 μg/kg each; a basal BUP-i of 0.4 μg/kg/h + MO-b of 5 μg/kg each; or a basal MO-i of 10 μg/kg/h + BUP-b of 0.15 μg/kg each. Bolus doses were delivered by intravenous patient-controlled analgesia, with a bolus lockout time of 7 minutes. Diclofenac 75 mg IM q6h was available as rescue pain medication. Every 15 minutes during the first 2 postoperative hours and hourly thereafter, patients used visual analog scales to rate their pain (from 0 = totally free of pain to 10 = unbearable pain), level of sedation (from 1 = totally awake to 10 = heavily sedated), and satisfaction with treatment (from 1 = totally unsatisfied to 10 = fully satisfied). Blood pressure, heart rate, respiration rate, and arterial blood oxygen saturation (SpO2) were monitored, and adverse effects reported by patients or noted by clinicians were recorded at the same times. Study end points included total opioid consumption (infusion + boluses), demand:delivery ratio, and use of rescue medication.

Results: One hundred twenty patients (63 men, 57 women; age range, 21–80 years; weight range, 40–120 kg) were included in the study. Seventy-four percent had other mild, treated diseases (American Society of Anesthesiologists physical class 2). Pain visual analog scale ratings were comparably high in all groups during the first 2 postoperative hours. Pain intensity ratings at 3 to 12 hours were significantly lower in those who received BUP-i + BUP-b compared with the other treatment groups (P = 0.018). The drug requirement during the postoperative period decreased significantly in all groups (P = 0.01); however, there was a significant difference between groups in the demand:delivery ratio at 3 to 12 hours (group *
drug interaction, $P = 0.026$). The numerically lowest demand:delivery ratio was seen with BUP-i + BUP-b. BUP-i was associated with a significantly lower heart rate compared with the other groups ($P = 0.027$); there were no drug-related differences in respiration rate, $SpO_2$, or sedation. Patients’ level of satisfaction with treatment was significantly higher in the group that received BUP-i + BUP-b compared with the other 3 groups ($P < 0.001$). Postoperative nausea and vomiting were mild and occurred at a similar incidence in all groups, as did rescue diclofenac use.

**Conclusions:** In these patients undergoing abdominal surgery, the BUP-i + BUP-b regimen controlled postoperative pain as well as did MO-i + MO-b or the combinations of BUP and MO. BUP neither inhibited the analgesia provided by MO nor induced undesired sedation or hemodynamic or respiratory effects. (Clin Ther. 2009;31:527–541) © 2009 Excerpta Medica Inc.

**Key words:** pain, postoperative, morphine, buprenorphine, IV PCA, infusion, bolus.

**INTRODUCTION**

Intravenous patient-controlled analgesia (IV PCA) enables optimal control of postsurgical pain and is associated with high levels of patient satisfaction, wakefulness, and cooperation. Morphine (MO) is the most commonly used agent in IV PCA protocols. However, the opioid adverse effects associated with MO (eg, sedation, respiratory depression, pruritus, nausea and vomiting) continue to pose a problem. Buprenorphine (BUP) is a semisynthetic, highly lipophilic opioid derived from thebaine. It partially agonizes the $\mu$-opioid and opioid receptor-like 1 receptors and fully antagonizes the $\kappa$- and $\delta$-opioid receptors. BUP has higher affinity for—and thus stronger binding to—$\mu$-opioid receptors than for other opioid receptors; however, it has lower intrinsic activity than do full $\mu$-opioid-receptor agonists such as MO, whereas its drug-receptor dissociation rate is comparatively slower. BUP is considered 25 to 50 times more potent than MO, and BUP 0.3 to 0.4 mg (administered intramuscularly or intravenously) is considered equianalgesic to MO 10 mg. The most important adverse effects reported with BUP administered intermittently by the intravenous or intramuscular route or by continuous intravenous infusion are respiratory depression, sedation, and hemodynamic instability. Escalating BUP doses have been reported to induce tolerance to BUP and cross-tolerance with MO in rats.

These pharmacologic properties have led to concerns about a possible interaction between BUP and other $\mu$-opioid-receptor agonists or antagonists and hence reluctance to use BUP as a postoperative analgesic, even though these concerns have not been supported by substantial prospective clinical data. In clinical studies, concomitant administration of intrathecal MO (4.3 $\mu$g/kg) and intravenous BUP (1.3 $\mu$g/kg) was associated with a prolonged antinociceptive state, and 46% fewer untoward effects were reported with the combination than with either agent alone. These results contradicted earlier claims that coadministration of MO and BUP would inhibit the antinociceptive effects of the individual agents. To date, there appear to be no randomized prospective studies in the literature that have compared the analgesic effect of BUP and MO alone or in combination as an option for IV PCA for postoperative pain control.

The present study compared the analgesic effect of BUP and MO separately and in combination for postoperative pain control. It was hypothesized that because of its higher receptor potency relative to MO, BUP would provide good analgesia (primary goal) with an acceptable adverse-effect profile (secondary goal) when administered in combination with MO via IV PCA at doses lower than those administered previously (MO 5 mg + BUP 0.15 mg [first bolus] and 1.2 mg + 0.04 mg [subsequent boluses], respectively).

**PATIENTS AND METHODS**

**Inclusion and Exclusion Criteria**

The study enrolled patients who were scheduled for major abdominal surgery at the Tel Aviv Sourasky Medical Center during 2006. Eligible patients were aged 18 to 80 years and were undergoing gastrectomy, large bowel resection, or partial pancreatectomy. Candidates were approached during the preoperative anesthesia examination and were given a full explanation of the study’s aims, the study medications, and the IV PCA device. Consenting patients provided written informed consent. The study protocol and informed-consent form were approved by the institutional review board.

Exclusion criteria included a history of drug or alcohol abuse, psychiatric disturbance, senile dementia, Alzheimer’s disease, seizures, suicide risk, use of psy-
chototropic drugs, and hypersensitivity to BUP, MO, NSAIDs, or their excipients. Patients receiving antide-
pressants, anticonvulsants, or muscle relaxants were
excluded, as were those who had taken a monoamine
oxidase inhibitor within 2 weeks of surgery. Also ex-
cluded were patients with chronic or acute pain of any
origin, respiratory failure or insufficiency, uncompens-
sated or congestive heart failure or hepatic failure, and
those scheduled for an emergency or palliative proce-
dure. A pregnancy test was performed at screening in
all premenopausal women; women who were preg-
nant or nursing were excluded.

Anesthesia and Surgery Management

Anesthesia and surgery were performed by the same
team, although intraoperative care was not controlled.
All patients were premedicated with oral diazepam
10 mg the night before and 40 to 75 minutes before
surgery. Within 1 to 2 minutes after intravenous ad-
ministration of a sedative dose of midazolam (1.5–
2 mg) and fentanyl (1.5 µg/kg), propofol (1–2 mg/kg)
was injected intravenously until the patient lost con-
sciousness. A nondepolarizing muscle relaxant was
administered to enable endotracheal intubation. All
study patients were mechanically ventilated.

General anesthesia was maintained according to
the institution’s protocol using nitrous oxide/oxygen
2/1 L/min enriched with isoflurane, with the goal of
delivering 1 minimal anesthetic concentration. The
nondepolarizing muscle relaxant and fentanyl were
infused continually or given by repeated doses to main-
tain muscle relaxation and analgesia, as well as hemo-
dynamic and ventilatory stability. Standard periopera-
tive monitoring included 5-lead electrocardiography
and noninvasive measurement of systolic blood pres-
bure (SBP) and diastolic blood pressure (DBP), heart
rate (HR), respiration rate (RR), end-tidal carbon di-
oxide concentration (when available), and arterial
blood oxygen saturation (SpO₂), measured by fingertip
pulse oximetry (AS/3 Compact Patient Monitor, Datex-
Ohmeda, Helsinki, Finland). Intraoperative adminis-
tration of fluids and blood replacement followed common
cardiovascular, renal, and laboratory indices.

All intraoperative drugs were stopped toward the end
of the procedure, and minimal doses of atropine and
neostigmine were administered to reverse muscle relaxa-
tion and allow the return of spontaneous respiration. All
patients were then transferred to the Post-Anesthesia
Care Unit (PACU) for 24 hours of close observation.

Study Design

This was a prospective, randomized, double-blind
trial. At the completion of surgery, a computer-generated
list was used to allocate patients to receive 1 of 4 proto-
cols (prepared by the hospital pharmacist) for 12 hours:
a basal BUP infusion (BUP-i) of 0.4 µg/kg/h + BUP boluses (BUP-b) of 0.15 µg/kg each; a basal MO in-
fusion (MO-i) of 10 µg/kg/h + MO boluses (MO-b) of
5 µg/kg each; a basal BUP-i of 0.4 µg/kg/h + MO-b of
5 µg/kg each; or a basal MO-i of 10 µg/kg/h + BUP-b of
0.15 µg/kg each (Figure 1). Bolus doses were deliv-
ered by IV PCA.

BUP, which is approved for postoperative pain
control in Europe but not in the United States, was
donated by the manufacturer.

The dosages chosen for this study were based on
previously reported pain control studies in which low
doses of BUP (a 30-mg bolus every 5 minutes) pro-
vided satisfactory reduction or elimination of pain
along with acceptable tolerability compared with
high doses (0.4 mg/70-kg bolus). The lowest studied
dose of BUP administered via IV PCA for the man-
agement of acute postoperative (laparotomy) pain was
85 µg (total) in the first hour, followed by 30 µg/h,
which was reported to provide adequate pain control
for the next 17 hours. In a randomized trial in pa-
tients undergoing lumbar spinal fusion who received
postoperative IV PCA (30 µg/bolus, with a 5-minute
lockout time) without a continuous infusion, the cu-
mulative dose over the 6 consecutive hours of the study
was 270 µg. In the present study, a smaller bolus dose
of 10 µg/bolus (7-minute lockout time) was chosen,
along with a basal infusion of 28 µg/h. The doses were
divided into basal (infusion) and demand (bolus) por-
tions on a body-weight basis to minimize the adverse
effects of BUP, mainly respiratory depression, while
providing adequate analgesia. The selected doses were
also consistent with the previously reported pharma-
cologic relationship between MO and BUP. MO
was chosen as the comparator because it is the most
commonly used agent in postoperative IV PCA.

Study Drug Administration

In the PACU, each patient was connected to an
oxygen face mask and a vital signs monitor. At the
first complaint of moderate to severe pain at rest

*Trademark: Temgesic Injection® (Reckitt Benckiser Healthcare Ltd., Hull, United Kingdom).
Figure 1. The 4 study protocols. BUP = buprenorphine; MO = morphine.

(5–10 on a visual analog scale [VAS]) and after the PACU attending physician, who was blinded to study-drug allocation, had established that the patient was coherent and cooperative, a PCA system consisting of 2 devices was connected to the patient’s intravenous line. The physician started the basal infusion of the assigned drug, and the first bolus was administered 5 minutes later via the second device. Subsequent boluses were administered by the patient. A 7-minute lockout time after administration of each bolus prevented excessive dispensing of drug. The physician could administer 2 additional boluses (applying the specified lockout time) during the first postoperative hour if required for optimal pain control. Rescue diclofenac 75 mg IM could be administered once in the PACU to begin analgesia during the initial opioid titration; thereafter, it could be administered every 6 hours. No hourly dose limit was set on any of the 4 drug protocols. All patients were treated according to the study protocol for 12 hours, after which they received standard pain care in the relevant surgical department.

Patients were discontinued from the study if they required immediate postoperative artificial ventilation lasting over 4 hours, if they were incoherent or experienced continuous sedation (VAS rating ≥5–10), exhibited combative behavior in the PACU, or required postoperative reintervention and/or transfer to the intensive care unit. If a patient was discontinued from the study, another suitable patient was recruited. Patients who were discontinued because of a protocol violation, patient’s decision, or ineffectiveness of study drug were not replaced.

**Study Assessments**

Every 15 minutes during the first 2 postoperative hours and hourly thereafter, patients used a VAS to rate their pain (from 0 = totally free of pain to 10 = unbearable pain), level of sedation (from 1 = totally awake to 10 = heavily sedated), and satisfaction with treatment (from 1 = totally unsatisfied to 10 = fully satisfied) (Table I). Blood pressure, HR, RR, and SpO₂ were monitored, and adverse effects reported by patients or noted by clinicians were recorded at the same times.

**Statistical Analyses**

The data were analyzed at the Statistical Laboratory of the School of Mathematics, Tel Aviv University, using SPSS for Windows version 14.01 (SPSS Inc., Chicago, Illinois). A pre study power table in which δ (the mean 6- to 9-hour difference in pain score from a separate pilot study) was set at 1.8, α at 0.05, and power at 0.95 determined a need for a minimum of 15 patients per group. Concomitant analysis of pain VAS ratings and PCA use required a minimum of 25 patients. Demographic data (age, weight), baseline clinical characteristics (HR, RR, SpO₂, SBP, DBP), American Society of Anesthesiologists physical class, duration of surgery, and intraoperative fentanyl use were compared using 1-way analysis of variance (ANOVA). Sex was ana-
Table I. Components of the efficacy and safety evaluations.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mode of Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
</tr>
<tr>
<td>Patient-rated pain</td>
<td>VAS from 0 = totally free of pain to 10 = unbearable pain</td>
</tr>
<tr>
<td>Patient-rated sedation</td>
<td>VAS from 1 = totally awake to 10 = heavily sedated</td>
</tr>
<tr>
<td>(patient was awakened if sleepy; if not rousable, no data were recorded at that time point)</td>
<td></td>
</tr>
<tr>
<td>Patient-rated satisfaction with treatment</td>
<td>VAS from 1 = totally unsatisfied to 10 = fully satisfied</td>
</tr>
<tr>
<td>Total opioid consumption</td>
<td>Infusion + boluses</td>
</tr>
<tr>
<td>PCA demand:delivery ratio</td>
<td>Ratio</td>
</tr>
<tr>
<td>Rescue medication use</td>
<td>Request for diclofenac 75 mg IM</td>
</tr>
<tr>
<td><strong>Safety/tolerability</strong></td>
<td></td>
</tr>
<tr>
<td>Hemodynamic/respiratory parameters</td>
<td>Blood pressure, heart rate, respiration rate, SpO₂ (fingertip pulse oximetry)</td>
</tr>
<tr>
<td>Adverse-effect rate</td>
<td>Hourly questioning of patient, medical staff notes</td>
</tr>
</tbody>
</table>

VAS = visual analog scale; PCA = patient-controlled analgesia; SpO₂ = arterial blood oxygen saturation.

**RESULTS**

Of the 126 patients originally screened, 6 were excluded. Thus, 120 surgical patients (30 per arm; 100% white) were randomized to treatment, all of whom completed the study (Figure 2). There were no significant differences between groups with respect to the distribution of types of major abdominal surgery (data not shown), demographic or clinical characteristics, or intraoperative data (Table II). Vital signs and patient-rated pain, sedation, and satisfaction were similar in all groups before connection of the IV PCA device. All patients were coherent before starting the study.

**Drug Use**

The amount of drug delivered by infusion was weight dependent, so the amount of BUP infused was similar in both BUP-i groups and the amount of MO infused was similar in both MO-i groups. The mean total amounts of opioid (infusion + bolus) delivered in the first 2 hours after surgery in the 2 single-drug protocols were 2-fold those delivered over 3 to 12 hours after surgery ($P < 0.03$). Although the difference was not statistically significant, the amounts of BUP delivered by bolus were 33% lower in patients assigned to the BUP-i + BUP-b protocol compared with the MO-i + BUP-b protocol; the amounts of MO delivered by bolus were also numerically lower in patients assigned to the BUP-i + MO-b protocol compared with the MO-i + MO-b protocol (Table III).

The demand:delivery ratios at 3 to 12 hours were significantly different between groups (group * drug interaction, $P = 0.026$) (Table III). The BUP-i + BUP-b protocol was associated with a numerically lower ra-
Screened for eligibility (N = 126)

Excluded (n = 6)
Postoperative ICU admission (4)
Surgery cancelled due to cardiac arrest (1)
Intraoperative and postoperative bleeding, leading to hemodynamic instability (1)

Randomized (n = 120)

Allocated to and received BUP infusion (n = 60)

Allocated to and received MO infusion (n = 60)

Analyzed (n = 60)

Analyzed (n = 60)

Figure 2. CONSORT diagram. ICU = intensive care unit; BUP = buprenorphine; MO = morphine.

At 3 to 12 hours after surgery (P < 0.001) (Figure 3). Specifically, pain ratings were significantly lower in patients who received BUP-i compared with those who received MO-i (P = 0.018). BUP-b was associated with numerically better pain ratings when combined with BUP-i rather than MO-i (Figure 4). Pain VAS ratings were significantly lower in the group that received BUP-i + BUP-b (P = 0.04).

Sedation and Satisfaction
Patient-rated sedation improved steadily and similarly among the 4 groups over the course of the study.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BUP-i + BUP-b (n = 30)</th>
<th>MO-i + MO-b (n = 30)</th>
<th>BUP-i + MO-b (n = 30)</th>
<th>MO-i + BUP-b (n = 30)</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>61.6 (10.2)</td>
<td>63.1 (15.2)</td>
<td>61.0 (13.2)</td>
<td>64.4 (9.5)</td>
<td>0.70</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>73.3 (18.2)</td>
<td>69.8 (12.5)</td>
<td>67.9 (13.5)</td>
<td>70.2 (12.8)</td>
<td>0.54</td>
</tr>
<tr>
<td>Age group, no. of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>≤65 y</td>
<td>15</td>
<td>16</td>
<td>15</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>65–80 y</td>
<td>15</td>
<td>14</td>
<td>15</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Sex, no. of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>15</td>
<td>14</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>15</td>
<td>16</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>ASA physical class, no. of patients</td>
<td></td>
<td></td>
<td></td>
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<td>0.76</td>
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<tr>
<td>1</td>
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<td>22</td>
<td>20</td>
<td>22</td>
<td>25</td>
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<td>3</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Type of surgery, no. of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>Small/large bowel resection</td>
<td>16</td>
<td>21</td>
<td>16</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Pancreatectomy</td>
<td>6</td>
<td>3</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Intraoperative fentanyl, mean (SD), µg/patient</td>
<td>423.3 (169.0)</td>
<td>463.3 (216.5)</td>
<td>446.7 (227.9)</td>
<td>444.2 (226.4)</td>
<td>0.91</td>
</tr>
<tr>
<td>Surgery time, mean (SD), min</td>
<td>186.5 (92.4)</td>
<td>208.5 (103.0)</td>
<td>164.2 (69.7)</td>
<td>192.3 (90.0)</td>
<td>0.29</td>
</tr>
<tr>
<td>Baseline vital signs, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>74.2 (11.9)</td>
<td>73.7 (10.9)</td>
<td>79.4 (10.6)</td>
<td>77.4 (10.9)</td>
<td>0.16</td>
</tr>
<tr>
<td>Respiration rate, breaths/min</td>
<td>15.3 (2.7)</td>
<td>14.9 (2.6)</td>
<td>15.4 (2.9)</td>
<td>14.9 (2.2)</td>
<td>0.82</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>137.3 (21.2)</td>
<td>140.9 (20.4)</td>
<td>139.7 (28.1)</td>
<td>133.4 (20.5)</td>
<td>0.63</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>77.8 (8.9)</td>
<td>75.4 (12.5)</td>
<td>74.5 (13.7)</td>
<td>74.1 (10.9)</td>
<td>0.64</td>
</tr>
<tr>
<td>SpO₂, %</td>
<td>96.7 (2.0)</td>
<td>97.2 (1.6)</td>
<td>97.1 (2.0)</td>
<td>97.1 (2.0)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

BUP-i = buprenorphine infusion; BUP-b = BUP bolus; MO-i = morphine infusion; MO-b = MO bolus; ANOVA = analysis of variance; ASA = American Society of Anesthesiologists; SpO₂ = arterial blood oxygen saturation.
Table III. Use of study drug and rescue medication, level of sedation, hemodynamic and respiratory parameters, and postoperative nausea and vomiting (PONV).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BUP-i + BUP-b</th>
<th>MO-i + MO-b</th>
<th>BUP-i + BUP-b</th>
<th>MO-i + MO-b</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid amount (infusion + bolus), µg/70 kg*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 2 h</td>
<td>98 (43)</td>
<td>3065 (1443)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Range</td>
<td>43–217</td>
<td>889–5354</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3–12 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>45 (29)*</td>
<td>1825 (941)*</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Range</td>
<td>23–98</td>
<td>548–4050</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cumulative 3- to 12-h bolus amount, mean (SD), µg</td>
<td>135 (123)</td>
<td>7445 (5943)</td>
<td>5139 (4718)</td>
<td>178 (159)</td>
<td>0.25</td>
</tr>
<tr>
<td>Demand:delivery ratio per group, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 2 h</td>
<td>3.29 (2.29)</td>
<td>4.58 (3.58)</td>
<td>5.36 (6.29)</td>
<td>7.28 (8.27)</td>
<td>0.63</td>
</tr>
<tr>
<td>3–12 h</td>
<td>2.27 (1.62)*</td>
<td>2.96 (2.04)*</td>
<td>3.57 (2.80)*</td>
<td>3.72 (3.27)*</td>
<td>0.03</td>
</tr>
<tr>
<td>Rescue diclofenac use, no. of events</td>
<td>23</td>
<td>21</td>
<td>18</td>
<td>22</td>
<td>0.36</td>
</tr>
<tr>
<td>Sedation level over 12 h (VAS), mean (SD)</td>
<td>3.07 (1.74)</td>
<td>3.24 (2.00)</td>
<td>3.14 (1.69)</td>
<td>2.96 (1.60)</td>
<td>0.24</td>
</tr>
<tr>
<td>Respiration rate over 12 h, mean (SD), breaths/min</td>
<td>16.4 (2.6)</td>
<td>16.4 (2.7)</td>
<td>15.7 (2.2)</td>
<td>16.2 (2.1)</td>
<td>0.30</td>
</tr>
<tr>
<td>SpO₂ over 12 h, mean (SD), %</td>
<td>96.8 (2.3)</td>
<td>96.8 (2.4)</td>
<td>96.7 (4.4)</td>
<td>97.2 (2.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>PONV, no.</td>
<td>7</td>
<td>5</td>
<td>10</td>
<td>6</td>
<td>0.36</td>
</tr>
<tr>
<td>Antiemetic use, no. of events</td>
<td>15</td>
<td>11</td>
<td>13</td>
<td>6</td>
<td>0.22</td>
</tr>
</tbody>
</table>

BUP-i = buprenorphine infusion; BUP-b = BUP bolus; MO-i = morphine infusion; MO-b = MO bolus; ANOVA = analysis of variance; VAS = visual analog scale; SpO₂ = arterial blood oxygen saturation.

*To allow comparison, drug amounts were adjusted to 70 kg body weight.

†P = 0.01 versus the corresponding ≤2-hour period, t test.
‡P = 0.026 versus the corresponding ≤2-hour period, t test.
§P < 0.001 versus the corresponding ≤2-hour period, t test.
There was an overall negative correlation between the mean sedation rate and the mean pain rating ($r = -0.182; P = 0.046$). Satisfaction with pain control was higher in the group that received BUP-i + BUP-b than in the other 3 groups (group * time interaction, $P < 0.001$) (Figure 5). There was a negative correlation between the log of the sum of 12-hour drug usage and mean satisfaction levels in all 4 groups ($r = -0.21; P = 0.023$).

**Respiratory Parameters**

No differences were found between groups with regard to RR or SpO$_2$. All groups had a significant increase in RR during the first 2 postoperative hours ($P = 0.001$) that decreased over time, indicating awakening. There was no occurrence of respiratory depression (<6 breaths/min$^{27}$). SpO$_2$ during spontaneous ventilation was also comparable in all groups, increasing during the first 2 hours (probably indicating gradual awakening) and decreasing slightly from 6 to 8 hours (time effect, $P < 0.001$) (data not shown).

**Hemodynamic Parameters**

All groups had minimal fluctuations in HR during the first 2 hours in the PACU, probably as a result of emergence from anesthesia, that later stabilized (time effect, $P < 0.001$). However, values were significantly lower in the BUP-i + BUP-b group than in the other 3 groups (HR * drug infusion * bolus interaction, $P = 0.027$).

SBP was significantly increased in all groups on arrival in the PACU as patients awakened from anesthesia (mean, +15 mm Hg) and subsequently decreased (time effect, $P < 0.001$). The 2 groups that received BUP-i had a decrease in DBP in the 3- to 12-hour postoperative period (drug infusion * time * DBP interaction, $P < 0.001$) that was not seen in the groups that received MO-i. During the first 9 hours, there was a significantly greater decrease in DBP in the BUP-i groups than in the MO-i groups ($P = 0.001$), with subsequent stabilization. No patient had an SBP <80 mm Hg, DBP <40 mm Hg, or HR <40 beats/min at any time during the study.
Adverse Effects

There were no significant differences between groups in the incidence of postoperative nausea and vomiting (PONV) (Table III). Twenty-eight episodes of PONV (38% of all 73 cases) occurred within 2 hours after surgery. These episodes were short-lived and responded to treatment with metoclopramide 10 mg or granisetron 4 mg.

There was 1 case of pruritus in the BUP-i + BUP-b group that occurred 5 hours after initiation of IV PCA. The pruritus was alleviated by promethazine (25 mg IV), which is commonly used for this indication in Israel. No patient experienced dizziness, agitation, or confusion.

DISCUSSION

Based on a search of MEDLINE, this 4-arm, randomized, double-blind, parallel-group study appears to be the first to have compared the clinical effects of BUP and MO, 2 pharmacologically different and reportedly antagonistic opioids, given by infusion and boluses (separately and in combination) for analgesia in the first 12 hours after major abdominal surgery. The results indicated that IV PCA with BUP alone or in combination with MO provided equivalent postoperative analgesia to IV PCA with MO alone in patients who had undergone major abdominal surgery. Pain intensity was rated lower in those receiving BUP-i + BUP-b, followed by BUP-i + MO-b, MO-i + BUP-b, and MO-i + MO-b. BUP did not negatively affect patient-rated levels of sedation or satisfaction, or hemodynamic or respiratory parameters. The group that received BUP-i + BUP-b had the lowest HR and DBP of the 4 groups. All groups had similar rates of adverse effects (PONV and pruritus), none of which put any patient at risk or caused drug-related discontinuations. Thus, at the analgesic doses and modes of administration used, BUP continued to be effective and was well tolerated when given both alone and in combination with MO, contradicting past reports of a negative interaction between BUP and other μ-opioid-receptor agonists/antagonists in animals and humans.
that might inhibit the antinociceptive effect of the individual drugs.\textsuperscript{14-16,20,29}

The primary goal of this study was to determine the antinociceptive efficacy of BUP delivered by IV PCA at the predetermined low infusion and bolus doses. In this respect, it differed from other studies that have used upward/downward titration, administration of high-dose boluses over a limited period, combinations of intramuscular and intravenous administration, and periodic dose limitation.\textsuperscript{11,30-33} The doses used in this study, which were 10\% to 15\% of those reported earlier,\textsuperscript{34} were adequate and effective based on the diminished need for bolus doses over time, the demand:delivery ratio, and the decrease in diclofenac use in the 3 to 12 hours after surgery. In addition, levels of satisfaction improved as pain levels decreased, and no patient asked to be withdrawn from the study. The higher amount of drug use in all groups during the first 2 postoperative hours compared with 3 to 12 hours after surgery probably represent recovery from anesthesia coupled with still low levels of blood drug concentrations,\textsuperscript{35} as well as supporting the efficacy of the drug protocols.

There is no common opioid dose for either BUP or MO that can be used in an efficacy comparison, apart from the wide range of equipotency data reported previously\textsuperscript{7,11}; the protocols used in this study fall within such ranges. The study did not aim to compare drug use per se, but rather to characterize the quality of analgesia obtained using weight-related infusions and boluses of both drugs alone and in combination. The rate of PCA implementation provides an objective assessment of the level of pain and drug efficacy.\textsuperscript{4,36} A low overall rate of use (low demand:delivery ratio)
indicated the effectiveness of all 4 protocols in providing analgesia. The numerically lowest demand:delivery ratio was seen in the BUP-i + BUP-b group, which also had the lowest mean pain values in the period from 3 to 12 hours after surgery; compared with MO-i + BUP-b, these results suggest the efficacy of the agonist/antagonist BUP-i protocol within known equianalgesic ratios. Moreover, no antagonism was noted when BUP and MO were used in combination, as indicated by the cumulative bolus doses. Animal experiments have described antagonistic interactions that were hypothesized to be caused by the partial-agonist properties of BUP at the μ-opioid receptor, which, in competition with a full agonist such as MO, would reduce the overall effect of BUP. The results of the present study are inconsistent with this assumption. Furthermore, the results are consistent with those from a study in rats by Kögel et al, who reported that an antinociceptive effect was achieved even when BUP given at analgesic doses was switched to a full μ-opioid-receptor agonist (MO, oxycodone, hydro­morphine, or fentanyl), with no loss of analgesic efficacy and no refractory period between the termination of BUP and the onset of action of the new regimen.

Low oxygenation and decreased minute ventilation are common physiologic occurrences in the early postoperative and postanesthesia period, resulting from incomplete awakening, opioid-induced sedation, or both. Hypoxia and uncontrolled pain may interfere with wound healing after major abdominal surgery. Optimal oxygenation and respiratory status are, therefore, essential. When using opioids, the risk of respiratory depression due to μ-opioid-receptor inhibition of respiratory control centers in the brainstem must be taken into account. BUP appears to be an exception in this respect. Animal studies have suggested a ceiling respiratory effect at increasing BUP doses. In healthy volunteers, BUP was associated with depression of minute ventilation that leveled off at doses ≥3.0 μg/kg (15-fold the dose used in the present study). Administration of BUP 4 μg/kg IM after orthopedic procedures conducted under fentanyl-balanced anesthesia was associated with severe respiratory depression requiring artificial ventilation. In orthopedic patients who were randomized in a 1:33 ratio to receive intramuscular BUP or MO, BUP was associated with a cumulatively longer duration of oxygen desaturation and more episodes of apnea per patient than MO. These effects were associated with the intramuscular mode of administration, which provides the least consistent blood drug concentrations. Finally, postoperative boluses of BUP 80 μg in patients who had undergone thoracotomy provided analgesia but were associated with respiratory depression.

Interestingly, in 50 women undergoing low-segment cesarean section, BUP at 0.4 to 7.0 mg IV per 24 hours was not associated with respiratory depression. In the present study, BUP and MO had comparable efficacy in maintaining adequate analgesia without having the effects on ventilation that have been reported in children. Whether this finding was related to the consistency of pharmacologic effect with the infusion compared with bolus-induced peaks, a ceiling effect of BUP on respiratory depression, attainment of optimal pain relief (and therefore better respiratory mechanics), the low dose, or the overall agonist/antagonist properties of BUP cannot be determined based on the study findings. Nevertheless, BUP appears to show promise for use in high-risk patients because of the absence of respiratory depression.

In cardiac patients undergoing surgery, maintenance of a lower HR and DBP has been recommended. In the present study, the BUP-i + BUP-b group had a 10% lower HR compared with the group that received other combinations of infusion + bolus; the difference was greatest compared with the group that received MO only. DBP was also low in the BUP-i + BUP-b group compared with the other groups. BUP has been reported to be associated with reductions from baseline in BP and HR in animals (10%–15%) and in children (10–12 beats/min). A lower and stable HR could be the effect of better analgesia achieved with BUP compared with MO or of partial μ-opioid-receptor blockade.

In a 3-day study in patients who had undergone cholecystectomy, BUP and MO were given as loading doses followed by boluses administered by IV PCA in a 1:13 ratio, with a 15-minute lockout time. A BUP loading dose (0.1–0.3 mg) followed by 0.1-mg boluses was associated with twice the rate of postoperative nausea on day 1 compared with an induced MO loading dose (2–4 mg) followed by 1-mg boluses (P = NS). Other studies have reported rates of pruritus, dizziness, and sweating with BUP that were 10% to 20% higher than those in the present study. BUP administered intravenously or caudally has been associated with high rates (50% and 80%, respectively).
and severity of PONV in children but not in adults. No patients withdrew from the present study, and all adverse effects were mild and tolerable, and responded rapidly to treatment. Use of low but effective BUP doses may partially explain the absence of severe adverse effects.

It is of clinical relevance that sedation decreased and satisfaction improved as pain was progressively controlled with BUP compared with MO alone or in combination. Moreover, no patients exhibited heightened anxiety. BUP has been reported to produce a maximal (ceiling) euphoric effect similar to that of MO 20 mg · 70 kg⁻¹. High sublingual doses of BUP (8 mg) have been associated with a plateau in terms of subjective and physiologic effects, unlike the orally administered full μ-opioid-receptor agonist methadone (allowing for a linear dose effect). The steady improvement in the level of sedation over time with BUP in this study was consistent with the findings of Capogna et al. The study findings are also consistent with reports that BUP was associated with less-intense opioid-induced dysphoria, probably because of its partial-agonist activity at μ-opioid receptors. The improvement in satisfaction may have been associated with a BUP-induced positive effect on mood and well-being via its κ-receptor activity.

Most published reports concerning the use of BUP for postoperative pain control come from studies in animals or healthy volunteers under overdose-like conditions and are quite old. Thus, no appropriate data appeared to be available with which to compare the results of the present study. In addition, as in other studies, the results were limited to the first 12 hours after surgery. A full 24 hours of data would have provided information on the first bowel movement and the time to removal of the urinary catheter. Finally, because of the inclusion and exclusion criteria, the results of this study are limited to the population studied.

CONCLUSIONS

In these patients who had undergone major abdominal surgery, BUP-i + BUP-b administered via IV PCA controlled postoperative pain in the first 12 postoperative hours as well as did MO-i + MO-b or the combinations of BUP and MO. BUP neither inhibited the analgesia provided by MO nor induced undesired sedation or hemodynamic or respiratory effects.

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