

The Effects of Residual Pain on Oxygenation and Breathing Pattern During Morphine Analgesia

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To determine the influence of pain on opioid-induced respiratory depression, we studied oxygenation and breathing patterns in 40 patients scheduled for knee surgery during postoperative patient-controlled analgesia (PCA). After 1 h of morphine PCA, patients were randomized to receive either 20 mL of placebo or bupivacaine 0.25% through a crural nerve catheter and allowed to use PCA for one more hour. Abnormal breathing events were identified and characterized by using the Edentrace II device (Nellcor, Jouy-en-Josas, France). The SpO_2 below which the patient spent 25% and 50% of a studied period was calculated (SpO_{2-25} , SpO_{2-50}). Pain relief with regional analgesia increased the incidence of abnormal respiratory events associated with oxygen

desaturation: during the second period, the pain score was lower in the bupivacaine group (0.7 ± 1 vs 4.1 ± 1.2), morphine consumption was larger in the placebo group (4.2 ± 1.3 vs 0.7 ± 1.4 mg), and there were more abnormal obstructive breathing events in the bupivacaine group (11 ± 16 vs 3.7 ± 4.3). SpO_{2-25} and SpO_{2-50} were lower in the bupivacaine than in placebo group ($91.5\% \pm 2.8\%$ vs $93.1\% \pm 2.1\%$, $92.9\% \pm 2.4\%$ vs $94.2\% \pm 1.8\%$). **Implications:** Pain relief with regional analgesia in patients previously treated with opioids increases the incidence of abnormal respiratory events associated with oxygen desaturation.

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Although the mechanisms by which pain modulates ventilatory control are unknown, clinical daily anesthesiology practice provides indirect evidence that pain stimulates ventilation, especially during emergence from anesthesia. Bourke (1) showed that, in patients with upper extremity injuries, relief of acute pain caused a reduction in the ventilatory response to CO_2 . Moreover, noxious or surgical stimuli increased minute ventilation during the administration of enflurane, isoflurane, and sevoflurane anesthesia (2–5). Recently, Sarton et al. (5) showed, in volunteers, that acute cutaneous pain of moderate intensity caused a tonic ventilatory drive.

The likelihood of pain's antagonizing specifically narcotic-induced respiratory depression seems high, but precise description of this antagonism is indirect or anecdotal. Hanks et al. (6) observed an unexpected respiratory depression after successful nerve block,

suggesting that pain relief had unmasked an opioid-induced respiratory depression. Further, Walsh (7) stated, without any specific reference, that the presence of pain is an antagonist to respiratory depression. This ability of pain to obviate the respiratory depressant effects of opioids has not been fully delineated. Therefore, the purpose of this study was to evaluate the respiratory effects of residual pain relief by regional analgesia during postoperative IV morphine patient-controlled analgesia (PCA).

Methods

We performed a double-blinded, randomized, placebo-controlled prospective study of 40 consecutive patients. Patients (ASA physical status I or II) undergoing elective knee surgery (ligamentoplasty or prosthesis) under general anesthesia were studied after obtaining approval by the local ethics committee and informed consent. Patients with any history of allergy to local anesthetics or morphine or cardiovascular, respiratory, hepatic, or renal disease were excluded. Patients considered to be heavy snorers by a bed partner's complaint or those with known sleep apnea were not included. Deviation from ideal body weight by more than 30% was also a noninclusion criterion. Enrolled tracheally extubated patients

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exhibiting hypoxic episodes defined by pulse oximetry as oxygen saturation less than 80% in room air at any time of the study were excluded, and nasal oxygen was immediately administered.

Patients were premedicated with 50 mg hydroxyzine given orally 1 h before being transferred into the operating room. Anesthesia was induced with 6–8 mg/kg thiopental, 0.1 mg/kg vecuronium, and 4 μ g/kg fentanyl IV. After tracheal intubation, general anesthesia was maintained with 0.6%–1% isoflurane (end-tidal concentration) and 50% nitrous oxide in oxygen. Additional boluses of fentanyl (1 μ g/kg) were administered to maintain surgical analgesia. Ventilation was adjusted to maintain end-tidal CO₂ partial pressure between 35 and 40 mmHg.

Before the induction of anesthesia, a perineural catheter was inserted during nerve stimulation control in the sheath of the crural nerve on the operated side. The patients were lying in the supine position with the extended limb maintained in a neutral position. A 50-mm insulated stimulating needle attached to the nerve stimulator was inserted in a cephalad direction 1 cm under the crural arcade and 1 cm externally to the femoral artery. The needle was advanced slowly until an evoked quadriceps contraction associated with patella clonus was observed. When this specific muscular response was continuously observed with a stimulating intensity ≤ 0.5 mA, the perineural catheter was inserted through the needle.

Preoperatively, the patients were given instructions about the use of a 10-cm visual analog scale (VAS) for postoperative pain evaluation and the use of a PCA device. The surgical time was defined as the time from surgical incision until arrival in the postanesthesia care unit. Anesthesia time was defined as the time from the anesthetic induction until extubation. The latency time was defined as the time between extubation and the start of PCA. When standardized criteria for extubation were met, the trachea was extubated, and patients were allowed to breathe spontaneously an oxygen/air mixture. On arrival in the postanesthesia care unit, patients were placed in a semirecumbent position. SpO₂ was monitored continuously.

During the latency time, respiratory measurements were performed before PCA administration, while patients were able to maintain an SpO₂ > 94% for 15 min without supplemental oxygen. As soon as pain was described as 7 cm or more on the VAS, an IV morphine PCA at a setting of 2 mg IV charge bolus, 1 mg per injection, with a 5-min lockout interval, was initiated. Two equal periods were then distinguished. During the first hour (P1), patients self-administered boluses of morphine. After P1, patients were randomly allocated to receive, in a double-blinded manner, 20 mL of placebo (NaCl 9%) or 0.25% bupivacaine through the crural nerve catheter. The second period (P2) started 15 min after the perineural injection, while patients

were allowed to use the PCA pump with the same baseline settings. Sedation (0 = awake tense, 1 = awake quiet, 2 = sedated arousable, 3 = sedated non-arousable) and VAS scores were determined every 15 min before and during PCA administration by two research nurses. Morphine consumption was recorded for the two periods.

Breathing patterns were analyzed using a portable sleep apnea screening device (Edentrace II; Nellcor, Jouy-en-Josas, France), which permits the measurements of nasal/oral airflow (thermistery), chest wall impedance, SpO₂ (finger probe), and their recordings (8,9). The data were downloaded to a personal computer for later analysis of respiratory events. All recorded respiratory values were referenced to values measured during the latency time. Abnormal breathing events (ABE) were defined as either complete cessation of airflow (apnea) or reduction ($\geq 50\%$) of respiratory airflow (hypopnea) lasting 10 s or more, accompanied by a decrease of 2% or more in SpO₂. Chest wall impedance was used to differentiate central to obstructive events. Obstructive ABE was defined as ABE with increased or normal respiratory effort, whereas ABE with absence of or reduced ($\geq 50\%$) respiratory effort was defined as central. The lowest SpO₂ was measured (SpO_{2,low}), and indices of oxygenation were calculated by plotting a histogram of saturation over the study period, then measuring the first lower quartile percentiles to determine SpO₂ 25% (SpO_{2,25}) and the two first quartile percentiles to determine SpO₂ 50% (SpO_{2,50}).

The injection of local anesthetics or placebo through the catheter and clinical data collection were performed by two independent observers. The same observers retrospectively analyzed records retrieved from portable sleep tracing.

Values are expressed as mean \pm SD in the text and in the tables and as mean \pm SEM in the figures. Anthropometric data, surgical time, anesthesia time, and latency time were compared by using a *t*-test for unpaired data. A two way analysis of variance was performed to compare indices of oxygenation, incidence of ABE, morphine consumption, and pain scores during the two periods of the study. The χ^2 test was used to compare the sedation score between the two groups. *P* values < 0.05 were considered significant. Computations of the data were performed using a statistical analysis system for a personal computer (JMP; SAS Institute, Cary, NC).

Results

Patient characteristics (age, weight, sex), duration of surgery, duration of anesthesia administration, and latency time were similar in the groups (Table 1). The duration of P1 was 63 \pm 4 min and 61 \pm 5 min, and the

Table 1. Demographic and Perioperative Data

	Group Placebo	Group Bupivacaine
Number (n)	19	16
Sex (M/F)	8/11	6/9
Age	56 ± 17	57 ± 16
Height (cm)	167 ± 9	169 ± 16
Weight (kg)	76 ± 9	75 ± 8
Body mass index (kg/m ²)	27 ± 4	26 ± 4
Surgical time (min)	156 ± 56	140 ± 40
Anesthesia time (min)	224 ± 100	205 ± 60
Time between last bolus of fentanyl and start of PCA (min)	95 ± 52	100 ± 44
Latency time (min)	70 ± 43	71 ± 24
Perioperative fentanyl (μg)	393 ± 204	428 ± 156

Values are mean ± sd.
PCA = patient-controlled analgesia.

duration of P2 was of 60 ± 2 min and 62 ± 3 min in the placebo and block groups, respectively. Total doses of perioperative fentanyl were the same in the groups (Table 1). One patient was excluded because of a low VAS score (maximum = 5.5) during the control period. Three patients were excluded from the study during P1 because of SpO_{2,low} values < 80%. One patient in the block group was retrospectively excluded because of a total lack of effect of the bupivacaine injection on the VAS score.

At the end of P1, the groups were similar regarding the intensity of pain. At the end of P2, VAS scores were significantly lower (*P* < 0.05) in patients who had received perineural bupivacaine than those in the placebo group (Figure 1). Sedation scores did not differ between the two groups throughout the study. Four patients had nausea (two in each group). None of the patients had pruritus. Before the perineural injection, PCA morphine consumption was similar in the groups. Patients in the placebo group self-administered more morphine (4.2 ± 0.3 mg) than those in the bupivacaine group (0.7 ± 0.3 mg) during P2 (Table 2).

The values of the lowest SpO₂ were not different for the two periods between the two groups. SpO_{2,low} was 89% ± 5% and 87% ± 5% during P1 and 88% ± 5% and 85% ± 6% during P2, respectively, for the placebo and bupivacaine groups. SpO_{2,25} and SpO_{2,50} were not different for the two groups during P1, whereas these two oxygenation indices were lower in the bupivacaine group during the second period of the study (Figure 2). The incidence of central and obstructive ABEs was similar for the groups during P1. During the second period of the study, the incidence of obstructive ABEs was significantly higher for the bupivacaine group, whereas the incidence of central ABE's was not different (Figure 3).

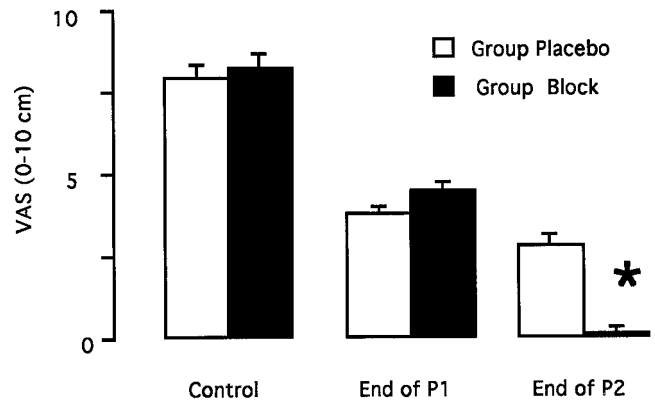


Figure 1. Visual analog scale (mean ± SEM). Before patient-controlled analgesia administration (control values) and at the end of P1, visual analog scale values were the same in the two groups. At the end of P2, values were significantly lower for group Bupivacaine than for Group Placebo (**P* < 0.05).

Table 2. Morphine Consumption During the Two Periods of the Study

	Group Placebo	Group Bupivacaine
Morphine consumption during P1 (mg)	8.9 ± 2	9.6 ± 2.1
Morphine consumption during P2 (mg)	4.2 ± 1.3	0.7 ± 1.4*

Values are mean ± sd.
P1 = patient-controlled analgesia period before block, P2 = patient-controlled analgesia period after block.
* *P* < 0.05 versus Group Placebo for P2.

Discussion

The principal finding of this study is that the abolition of nociceptive stimuli by crural nerve blockade after knee surgery revealed the respiratory depressant effect of morphine during PCA. Our data show that the total suppression of postoperative noxious stimuli increases the incidence of respiratory obstruction and desaturation events in patients treated with morphine. These results emphasize the interaction that links residual pain and respiratory pattern during morphine analgesia administration. Although some anecdotal reports have suggested that pain may counterbalance the respiratory depressant effect of morphine (6), no prospective study evaluating this phenomenon in humans has been undertaken until now.

In order to evaluate the influence of pain on breathing patterns, we studied patients whose surgery is known to be painful and not to alter respiratory function (10). Standard PCA settings were used for the control of pain in the first part of this study (11). During this first period, all patients required consistent doses of morphine given by autoadministration, which resulted in partial relief of pain, because the pain score was 5 cm on the VAS after one hour of PCA. Because our principal goal was to evaluate the

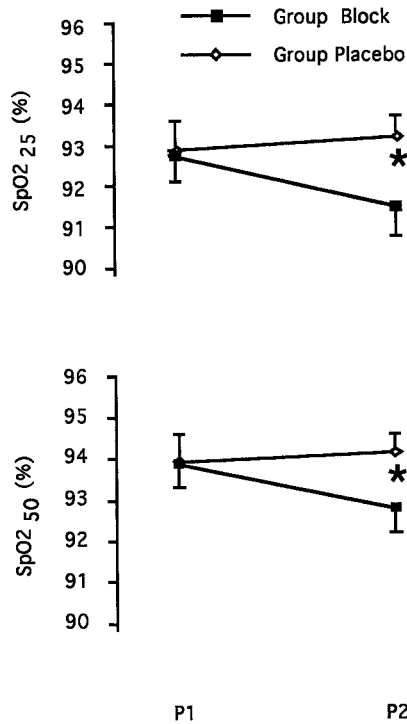


Figure 2. The effect of crural block on SpO₂ 25% (SpO₂₂₅) and SpO₂ 50% (SpO₂₅₀). SpO₂₂₅ and SpO₂₅₀ of Group Bupivacaine are lower than those of Group Placebo during P2 (**P* < 0.05).

effect of residual pain on the ventilatory pattern during morphine analgesia administration, the amount of morphine autoadministered by the patients during the second part of the study was considered as an indirect, but sensitive, index of the level of residual pain. During the second period of our study, the dramatic decrease of pain scores and morphine consumption in the block group attests to the efficacy of this type of analgesia (12), whereas in the placebo group, the level of residual pain and morphine requirement remained unchanged. In addition, several studies have shown that bupivacaine exerts no significant stimulatory effect on ventilation (13,14). Therefore, we are confident that the impairment of oxygenation indices observed in the second period for the bupivacaine group is not related to a pharmacodynamic effect of this drug.

Respiratory measurements were performed with the portable monitoring device (Edentrace II), which was initially designed for epidemiologic and laboratory studies of sleep-related breathing disturbances (8). This device, validated against full nocturnal polysomnography (9), allowed us to calculate semiquantitative oxygenation indices such as SpO₂₂₅ and SpO₂₅₀. We have considered that these oxygenation indices were more clinically relevant for qualifying respiratory depression than ventilatory response to CO₂ stimulation, which reflects the CO₂ sensitivity of the patients during a short period (13).

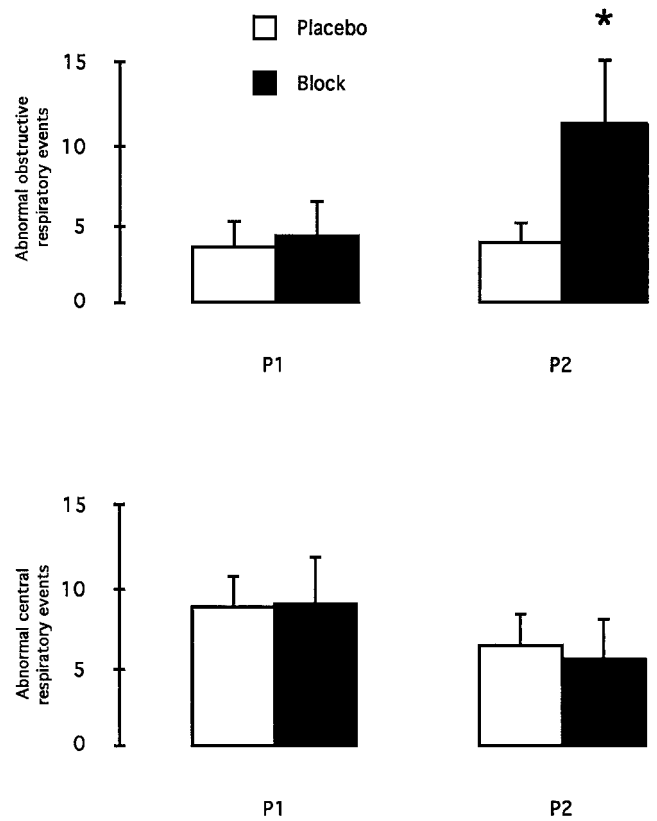


Figure 3. The incidence of abnormal respiratory events during P1 and P2. **P* < 0.05 compared with Group Placebo.

Morphine analgesia is frequently responsible for ventilatory disturbances during sleep in postoperative patients (15). Although our results could be at least partially explained by differences in the state of arousal between the two groups during P2, we were unable to document significant differences in sedation scores. Under the conditions of our study, continuous electroencephalographic monitoring would have been more accurate for differentiating arousal states between groups.

During the second period of the study, morphine consumption decreased dramatically in the bupivacaine group while obstructive events, in association with episodes of oxygenation desaturation, increased. The central depressant effect of opioids on respiration is well known (16). Although our technique of investigation is semiquantitative, we suggest that obstructive apnea is more likely to induce arterial oxygen desaturation than central apnea after morphine administration. Similar to our study, Catley et al. (15) observed that desaturation episodes in postoperative patients treated with morphine were mainly associated with obstructive apnea.

Few studies have investigated the relationship between pain and ventilation. In awake traumatized patients, the effect of acute pain on ventilatory control

has been studied. Bourke (1) showed that total abolition of acute pain from upper extremity injuries by axillary brachial plexus block reduced ventilatory CO₂ sensitivity. Sarton et al. (5) demonstrated, in healthy volunteers, that moderate acute pain (VAS scores between 4.5 and 5.5 cm on a 10-cm scale) increased baseline ventilation. Thus, although there is increasing evidence that pain is a respiratory stimulant, the mechanisms by which acute pain modulates ventilatory control are unknown. Our results show that acute pain could also act on the ventilatory pattern in awake patients who received morphine. We suggest that particular postoperative patient care be performed when locoregional analgesia techniques are combined with systemic opioids for pain relief.

In summary, we found that complete abolition of acute postoperative pain during morphine analgesia caused arterial oxygen desaturation and increased the incidence of ABEs. These results emphasize the importance of pain as a potent stimulator of the respiration in patients receiving central analgesics.

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