Respiratory depression following epidural morphine: a clinical study

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Thirteen post-thoracotomy patients were entered into a double-blind, randomized clinical trial comparing the effects of epidural morphine (Group E) and intravenous morphine (Group I) on postoperative respiratory depression.

Postoperative respiratory depression was assessed for 24 hours by (a) $PaCO_2$ at 2, 6, 12 and 24 hours (b) hourly assessment of respiratory rate (RR) (c) presence of respiratory rate of less than ten breaths per min for greater than 5 min (SRR) (d) hypopnoea/apnoea (H/A).

RR, SRR, and H/A were measured using respiratory inductive plethysmography. $PaCO_2$ was significantly elevated at 2, 6 and 12 hours in Group E and only at two hours in Group I. One of five patients in Group I had a single episode of SRR whereas five of eight patients in Group E had multiple episodes of SRR. None of the patients in Group I had H/A episodes, in contrast to six of eight in Group E who had numerous H/A episodes postoperatively. This difference was statistically significant.

Multiple doses of epidural morphine produce an insidious and unpredictable change in respiratory pattern. Electronic monitoring is useful to assess those at risk of overdose and possible respiratory arrest.

Key words
COMPLICATIONS: respiratory depression; ANALGESICS: morphine; ANAESTHETIC TECHNIQUES: epidural; VENTILATION: depression.

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Evidence is accumulating that epidural narcotics, like narcotics administered by other routes, are capable of producing profound and life-threatening respiratory depression.[1–6] We have shown that epidural morphine administered via a lumbar epidural catheter provides postoperative analgesia and improves postoperative respiratory function in patients undergoing thoracotomy.[7] In addition two patients in that study demonstrated CO_2 retention and increased somnolence after epidural morphine.[8] The current study was undertaken to clarify the occurrence and time course of respiratory depression after epidural morphine administration in the clinical model we previously used.[7]

Methods

Thirteen patients undergoing elective thoracotomy gave their informed consent for the study, which was approved by the Human Experimentation Committee of the University of Toronto. They were randomly allocated to two groups; one group received lumbar epidural morphine (Groupe E) and the other received intravenous morphine (Group I).

The epidural morphine was prepared as 5 mg powdered base in 20 ml preservative-free normal saline. Patient and observer blinding was achieved by injecting via both the intravenous and epidural routes whenever the patients required analgesia postoperatively. For the group receiving intravenous narcotics 0.05–0.07 $mg \cdot kg^{-1}$ morphine was injected intravenously and 20 ml of normal saline was injected epidurally, whereas the epidural group received 5 mg of morphine in 20 ml saline epidurally and 5 ml saline intravenously.

Instruments and calibration

The breathing pattern was continuously measured using a respiratory inductive plenthysmograph (RIP) that consisted of two transducer bands worn around

the rib cage and abdomen. A commercially available RIP (Respitrace 300SC, Ambulatory Monitoring Inc., New York) was used. The transducers measured changes in cross-sectional area independent of the shape of the torso.[10]

The signals from the transducers were fed into a microprocessor where they were electronically summed to give a third signal that was proportional to tidal volume. All three signals are then directed to a self-contained video monitor in the RIP. In addition the RIP is coupled with its own printer to provide hard copy graphics of sequences of data displayed on the video monitor or processed data which can be printed at programmed time intervals. All three signals were calibrated with the patient breathing into a wedge spirometer (Model 270 Med-Science, St. Louis, Missouri) which was itself calibrated with a one litre air syringe previously checked with volume displacement. One litre of air was adjusted to give one volt output from the spirometer. With the RIP attached data was collected while the patient was supine and breathing into the spirometer with a nose clip in place. After seven to eight breaths, further data were collected with the patient standing. The microprocessor then calculated two calibration factors using the least squares method,[22] one factor for the rib cage signal and the other for the abdominal signal. The corrected tidal volume was then validated with the patient breathing into the spirometer in the 45° head-up position to be used postoperatively. The validation program compares the corrected tidal volume to the spirometer input. The calibration factors were adopted for postoperative use if there was less than ten per cent error calculated by the validation program. Validation was repeated postoperatively to assess if recalibration was necessary.

After calibration the RIP was programmed to compute the following variables.

1 Respiratory frequency (RR). Mean respiratory frequency in normal subjects monitored non-invasively with RIP ranges from 16.6 to 17 breaths/minute.[23] The system was programmed to compute and record the mean respiratory frequency at 5 min intervals.
2 Slow respiratory rate (SRR).[14] Slow respiratory rate was defined as a respiratory frequency of less than 10/min for at least 5 min.
3 Hypopnoea/Apnoea (H/A). Tidal volumes of less than 90 ml lasting for 15 sec or longer were recorded as apnoea by the system. Although the default value of 90 ml indicates hypopnoea, not apnoea per se, postoperative visual observation of the signals in all cases showed that once a tidal volume of less than 90 ml was recorded, respiratory movements ceased.

The incidence of SRR and H/A was also recorded by the printer at 5 min intervals.

After calibration and programming of the RIP, preoperative data collection was done over a 15-min period. The position of the two RIP transducer bands was marked on the skin and the bands removed.

Anaesthesia

No preoperative medication was given. Immediately preoperatively, an epidural catheter was placed in either the L_{2-3} or L_{3-4} interspace. A test dose of 2 ml of two per cent carbonated lidocaine was given. Satisfactory placement of the catheter resulted in the patient receiving a total of 10 ml of two per cent carbonated lidocaine. Analgesia levels ranged between T_{10} and T_4. General anaesthesia was induced with thiopentone and either succinylcholine or pancuronium was administered to facilitate tracheal intubation. All patients were intubated with either a Robertshaw double-lumen tube or a single lumen tube and a bronchial blocker. All patients had radial artery catheters placed for blood pressure monitoring and arterial blood gas sampling.

Patients were ventilated with nitrous oxide and oxygen in varying concentrations to maintain adequate haemoglobin saturation and one-lung ventilation was conducted when necessary. In addition enflurane was used in varying concentrations to provide analgesia and hypnosis. At the end of surgery neuromuscular blockade was reversed with neostigmine and atropine. Once spontaneous ventilation was established the patients were taken to the recovery room. Due to the nature of the surgery all patients received supplemental oxygen by face mask for at least 24 hours at whatever concentration necessary to maintain an adequate arterial pO_2.

Postoperative analgesia

Due to the long latency of onset of epidural morphine for thoracic pain relief the first dose was given intraoperatively. Thus both intravenous (5 ml) and epidural (20 ml) vials were given simultaneously intraoperatively. Morphine was present in only

one of the vials as described above. Patients receiving intravenous morphine had been randomized preoperatively into the intravenous group (I) and continued to receive intravenous morphine throughout the postoperative period. Patients who had been randomized into the epidural group (E) received epidural morphine both intraoperatively and postoperatively. The individual administering the morphine was blind as to which vial (epidural or intravenous) contained the morphine. Only one dose of morphine was given intraoperatively.

An attempt was made to administer the morphine approximately one hour prior to the end of the operation. Unfortunately the timing of the procedure proved difficult to predict and thus there was a lack of uniformity in the elapsed time between the first dose of morphine and the cessation of anaesthesia. Nine of the 13 patients received the first dose during the last hour of anaesthesia. Three patients received the first dose 1.5–3.0 hours before the end of anaesthesia. One patient received the first dose only 20 minutes prior to the end of the anaesthesia. Further doses of morphine were given in the recovery room and in the ICU where the patients were monitored for the observation period of 24 hours. At least 30-minute intervals were allowed to elapse between each dose.

Postoperative measurements

Pain scores were obtained using a 10 cm horizontal linear analog scale (0 = no pain, 10 = severe pain).[9] Pain and arterial blood gases were measured at 2, 6, 12 and 24 hours postoperatively. The RIP coils were replaced around the chest and abdomen and aligned with the markings made preoperatively as soon as the patient reached the recovery room. The calibration factors previously derived were then entered into the microprocessor and the RIP monitored continuously from this point onwards, for 24 hours. The video monitor was oriented so as to be clearly seen by the observer. Changes in respiratory pattern were thus easily seen by the observer as well as being recorded on the printer at 5 min intervals.

The epidural and intravenous preparations were given for the first 24 hours and then the epidural catheter was removed. The patients were then given either intravenous or intramuscular morphine for analgesia. The patients were kept in the ICU for at least another 24 hours.

Data analysis

Fischers Exact Test (2-tail) and unpaired t-tests were used to examine preoperative values for the two groups. Unpaired t-tests were used to analyze postoperative respiratory rates, arterial blood gases and pain scores. Analysis of variance was used to determine significant differences between variables within each group at each point of measurement and between postoperative values. Fischer's Exact Test (2-tail) was used in the analysis of H/A and SRR. $P < 0.05$ was taken to indicate significant differences in all cases.

Results

Group I included three males and two females with a mean (± SD) weight of 73.8 ± 7.7 kg and mean age of 63.8 ± 7.9 yr. Group E included six males and two females with a mean weight of 73.5 ± 8 kg and a mean age of 53.0 ± 11.9 yr. There were no significant differences between the groups for age or weight.

The operative procedures were comparable for the two groups. Group I had three single lobectomies and two wedge resections. Group E included five single lobectomies and three exploratory thoracotomies without resection.

From the time of the first intraoperative dose until 24 hours after entry into the recovery room, Group E required significantly fewer injections (4.2 ± 0.5 vs 7.2 ± 0.7; $p < 0.03$) and a lower total dose of morphine (21.9 ± 2.1 mg vs 36.0 ± 3.7 mg; $p < 0.03$).

Pain relief attained was satisfactory for both groups with no statistical difference between groups (Table I).

Ventilation disturbances

$PACO_2$

The measured $PaCO_2$ and the changes in $PaCO_2$

TABLE I Linear analogue pain scores (mean ± SEM)

	Pain score		
Hours post-op	*Epidural group*	*Intravenous group*	*Significance*
2 h	5 ± 1	6 ± 1	NS
6 h	3 ± 1	4 ± 1	NS
12 h	4 ± 1	4 ± 1	NS
24 h	4 ± 1	4 ± 2	NS

NS = no significant difference between groups.

TABLE II Arterial PCO_2 (mean ± SEM)

	Actual $PaCO_2$		*$\Delta PaCO_2$*		
Hours post-op	*Epidural group*	*Intravenous group*	*Epidural group*	*Intravenous group*	*Significance between groups*
Preop	36 ± 3	35 ± 4	—	—	
2	49 ± 4*	45 ± 6*	13 ± 3*	10 ± 4*	NS
6	50 ± 4*	42 ± 5	14 ± 5*	7 ± 4	NS
12	47 ± 3*	42 ± 4	11 ± 3*	7 ± 3	NS
24	41 ± 1	40 ± 4	5 ± 4	5 ± 2	NS

$\Delta PaCO_2$ = difference between preoperative and postoperative mean values.
NS = No significant difference between groups.
* = Significantly different from preoperative value, within group ($p < 0.05$).

relative to the preoperative control values are shown in Table II. Group E had significantly elevated $PaCO_2$ levels at 2, 6 and 12 h compared to the preoperative level whereas Group I's $PaCO_2$ level was only significantly elevated at two hours postoperatively (Table II). Between-group analysis, however, showed no significant differences in $PaCO_2$ levels between Group E and Group I at 2, 6, 12 and 24 hours postoperatively.

RESPIRATORY FREQUENCY (RR)

The 5 min RR measurements were summed and averaged to give hourly respiratory rates which are shown in Figure 1. Group E had consistently lower RR than Group I. At only three time periods (3, 10, 18 h) postoperatively were the differences in RR significant.

SLOW RESPIRATORY RATE (SRR)

In Group I, one patient of five showed a single episode of SRR. However, in group E, five of eight patients showed multiple episodes of SRR. Due to the small size of the two groups, what is clearly a numerically large difference in occurrence of SRR between the two groups did not reach statistical significance.

HYPOPNOEA/APNOEA (H/A)

None of the patients in Group I experienced periods of H/A. In contrast six of eight patients in Group EP experienced periods of H/A at some time during the 24-hour postoperative period. Detailed analysis of the temporal relationship between the time of dose and the incidence of H/A and SRR for each of the six patients in Group E is shown in Figure 2 (A-F).

Discussion

Although the group of patients in this study was much smaller than that of our previous study[7] some of the findings are similar. Age, sex, weight, type of operation, mean doses of epidural and intravenous morphine were similar in both studies.[7] In addition, in this study there were no significant differences between the two groups with regard to pain relief or $PaCO_2$ at the times these variables were measured (Tables I and II). Within the groups, however, Group E had a longer lasting elevation of $PaCO_2$ from 2 to 12 hours postoperatively (Table II).

The most interesting results, however, are related to the use of respiratory inductive plethysomography which provided continuous monitoring of the patients' respiratory patterns and rates. Analysis of RR on an hourly basis does little except indicate consistently slower RR in the epidural group (Figure 1.).

Analysis of respiratory pattern, however, clearly showed that Group E was behaving differently than Group I. Six of the eight patients in Group E exhibited multiple periods of SRR and H/A (Figure 2) whereas only one patient in Group I revealed a single episode of SRR and no episodes of H/A. Whether the first dose of epidural morphine can produce SRR and H/A is not known, as the patients were still anaesthetized when they received their first doses. One patient demonstrated SRR and H/A after only two doses of epidural morphine (10 mg) whereas the remaining five patients had three doses of epidural morphine (15 mg) prior to the onset of SRR and H/A.

The long latency period between the injection of lumbar epidural morphine and the onset of pain

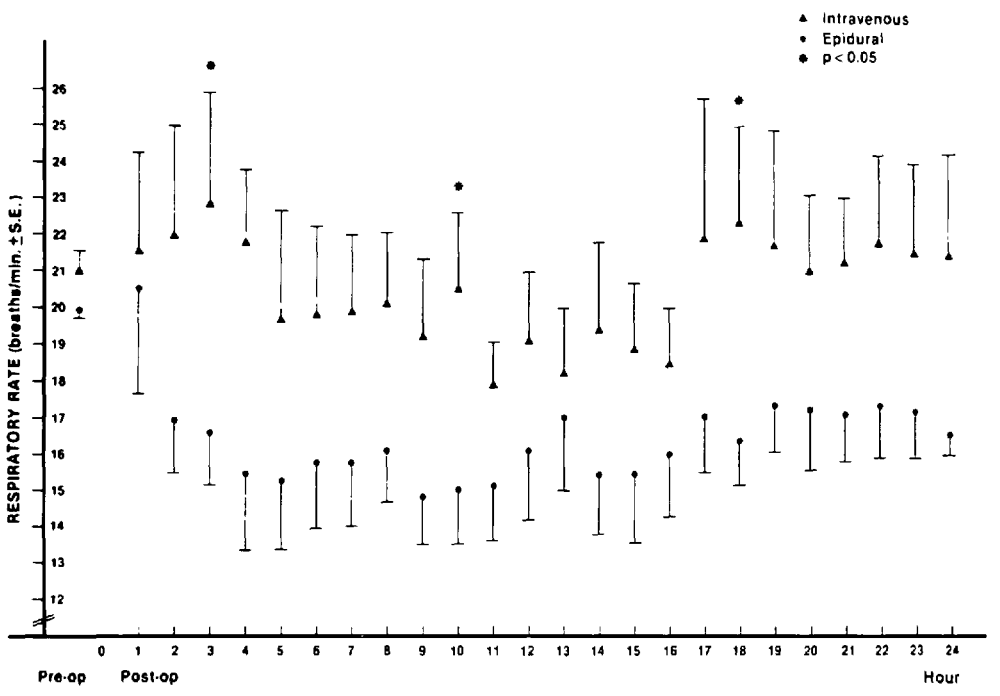

FIGURE 1 Respiratory rate for epidural and intravenous morphine groups (mean ± SEM).

relief in the thoracic dermatomes, coupled with the double-blind nature of this study, are the factors which led to the tendency to give several doses of morphine both in group E and group I early in the postoperative period. At least 30 min intervals were required between doses. However, only in patient (F) were four doses of epidural morphine (20 mg) given in close proximity over two to three hours (Figure 2-F). Not surprisingly this patient required only one futher dose at hour 20 (Figure 20-F). This patient demonstrated the highest incidence of SRR and H/A. In spite of this, $PaCO_2$ was 46 mmHg at 2 hr postoperatively, 54 at 5 hr, 60 at 7 hr, 54 at 10 hr and 42 at 24 hr. No ventilatory assistance or narcotic reversal was necessary. Arterial pH was never lower than 7.31. In contrast patient A had only two doses of epidural morphine (10 mg) and exhibited SRR and H/A three to eight hours later.

The lipophobic nature of morphine and the resulting long latency period before the onset of analgesia lead to relatively frequent early dosing in this study and this probably mirrors clinical experience with use of lumbar epidural catheters. The use of a lipophilic drug with rapid onset of epidural analgesia, such as fentanyl, before using epidural morphine may be one method of avoiding "loading" the epidural space with a lipophobic narcotic. Alternatively, placing an epidural catheter close to the surgical incision (in this case the mid-thoracic region) may decrease the morphine requirement and decrease the latency period before onset of analgesia.

The effect of *thoracic* epidural morphine on respiratory pattern is unknown. However, similar results to those reported here may occur, with even smaller doses of morphine, because of the closer proximity to the respiratory centre. In addition, the increased possibility of accidental spinal cord damage is a further hazard of thoracic epidural catheter insertion.

H/A could occur without SRR (patients D and E) but none of the six patients from Group E showed SRR without H/A. In addition, patients would demand pain relief at the same time periods in

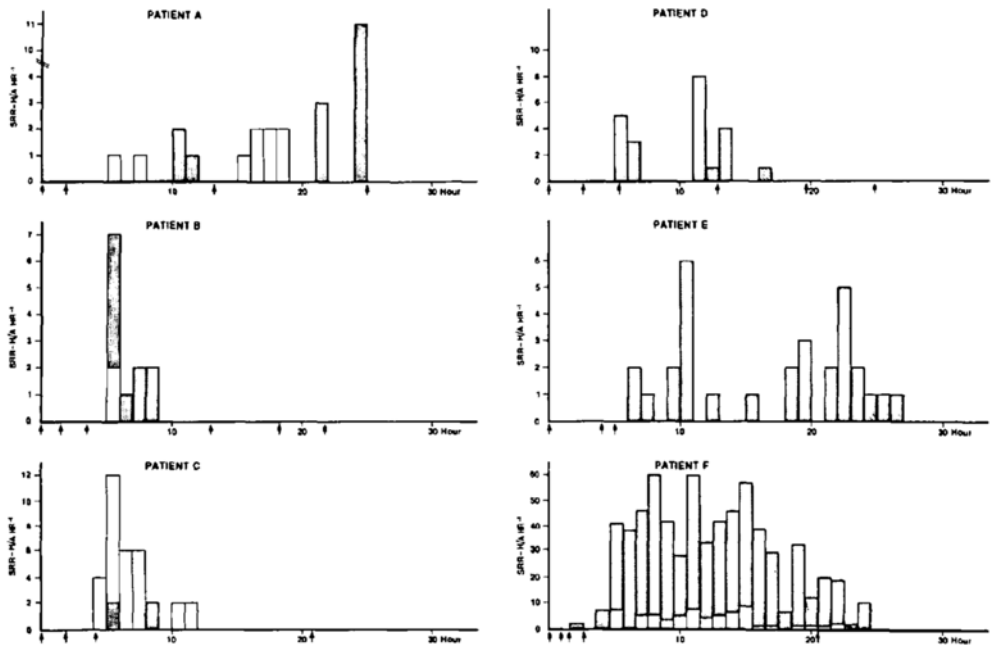

FIGURE 2 Each bar graph depicts the incidence of slow respiratory rate (SRR) (open bar) and hypopnoea/apnoea (H/A) (shaded bar) per hour in the six patients in the epidural group who had postoperative respiratory depression. Arrows (↑) indicate times of epidural morphine administration. The first dose was given intraoperatively (see text). Note the individual variation in dose requirements and incidence of SRR and H/A in the six patients. Also note the demand for analgesia at the same time as SRR and H/A occurred (patients A, D, F).

which SRR and H/A were occurring (patients A, C, D, F). In two of the patients (B, C) the episodes of SRR and H/A were clumped together soon after the third dose (Figure 2: B, C). By 10 to 12 hours the episodes of H/A and SRR had disappeared and did not recur in spite of further epidural doses (Figure 2: B, C). In the four other patients the episodes of SRR and H/A were distributed throughout the 24 hour postoperative period.

Visual observation of the respiratory pattern on the RIP monitor often showed periodic breathing analogous to a Cheyne-Strokes respiratory pattern in the patients receiving epidural narcotics. Apnoeic episodes were heralded by dimunition in tidal volume and were followed by increased tidal ventilation. All episodes of hyponoea-apnoea (H/A) were visually confirmed by the attending nurse or an investigator, as the monitor was placed adjacent to the nursing station.

The RIP has been used to assess the respiratory effects of narcotics administered systematically to postoperative patients.[12–14] Patients who received narcotics either by intravenous infusion[13,14] or intramuscular injection[12] demonstrated similar changes to those we have found with epidural morphine. These included episodes of obstructive apnoea, slow respiratory rate, small tidal volume and paradoxical breathing.[13,14] In addition while breathing room air episodes of oxygen desaturation occurred, 80 per cent of which occurred only during periods of sleep.

Post-thoracotomy patients in our study are continuously supplemented with humidified oxygen at a concentration necessary to prevent hypoxia. All arterial samples tested consistently revealed PaO_2 levels above 100 mmHg. Although it is only speculative as to whether hypoxia would develop in those patients with SRR and apnoea, the possibility is highlighted by the synergistic effect between morphine infusions and sleep in causing

severe respiratory disturbances postoperatively. The postoperative patient spends a large part of the time sleeping.[14]

The effect of epidural morphine on respiratory control has been studied in volunteers[15,16] and in postoperative patients[16–19,21] using CO_2 challenge techniques. All studies used a continuous epidural technique with lumbar insertion of the catheter. Doses ranged from 2 to 10 mg. No dose larger than 10 mg was given over a 24-hour period. All studies showed a dose-related depression of CO_2 response curves or CO_2–airway occlusion pressure responses.

Of interest is the study by Kafer *et al.*[17] which proposed a biphasic depression of control of ventilation by epidural morphine. This group found maximal depression of the CO_2–ventilation response at one to two hours after a single epidural injection of 0.1 $mg \cdot kg^{-1}$ of morphine and ascribed this early depression to absorption into epidural veins and circulatory redistribution to the brain. In addition only at eight hour post-injection was there further depression of the CO_2 ventilation response curves. At 4, 12, and 24 hours post-injection the response to CO_2 was unchanged. Respiratory depression occurring at eight hours was attributed to cephalad movement of morphine in the CSF.

In contrast, in our study no clear cut pattern emerged in the six patients showing SRR and H/A in the epidural group. This was probably due to the much larger dose required, and the repetitive nature of dosing needed to relieve the pain of a thoracotomy when a lumbar sited catheter is used. In addition some vascular absorption and recirculation of morphine occurs at this dose level[19–21] and may affect respiratory control. Unfortunately serum morphine levels were not measured.

As pointed out above, a major drawback of epidural morphine, particularly if injected at a lumbar site to provide upper thoracic analgesia, is the long latency (30–60 min) between administration and analgesia. This often leads to several doses being given before analgesia occurs. Whether SRR and H/A would occur after only one or two doses of epidural lumbar morphine in the 2–5 mg range is unknown.

The respiratory pattern changes revealed by the use of RIP are difficult to detect without the use of electronic monitoring and may well have been present in our previous study.[7,8]

Conclusion

Both intravenous and epidural morphine produced satisfactory postoperative analgesia. In addition both the intravenous and epidural groups demonstrated hypoventilation and raised $PaCO_2$ postoperatively. However, the epidural group demonstrated significantly more frequent changes in respiratory pattern and elevated $PaCO_2$ than did the intravenous group. The alterations in respiratory pattern in the epidural group were subtle and insidious in onset and unpredictable in duration. The fact that no patient in the epidural group required naloxone reversal or ventilator support should not detract from the inherent dangers posed by the use of postoperative epidural morphine. From our results the use of hourly respiratory rate to monitor the occurrence of respiratory depression with epidural morphine may be misleading. Continuous postoperative monitoring with simple apnoea monitors would seem to be useful for these patients, in addition to placing them in a postoperative area providing constant observation for at least 12 to 18 hours after their last dose of epidural morphine.

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Résumé

Treize patients ayant subi une thoracotomie ont été étudiés à double insu et d'une façon randomisée dans une étude clinique comparant les effets de la morphine épidurale (groupe E) et la morphine intraveineuse (groupe I) sur la dépression respiratoire post-opératoire.

La dépression respiratoire post-opératoire a été évaluée pour 24 heures par (a) la $PaCO_2$ à 2, 6, 12 et 24 heures, (b) l'évaluation à toutes les heures de la fréquence respiratoire (RR), (c) la présence d'une fréquence respiratoire inférieure à dix par minute pour une durée supérieure à cinq minutes (SRR), (d) l'hypopnée/apnée (H/A).

Les paramètres RR, SRR, et H/A ont été mesurés par l'intermédiaire de la pléthysmographie inductive respiratoire. La $PaCO_2$ était significativement plus élevée à 2, 6 et 12 heures dans le groupe E et uniquement à deux heures dans le groupe I. Un des cinq patients du groupe I a présenté un épisode unique de SRR alors que cinq des huit patients du groupe E ont présenté plusieurs épisodes de SRR. Aucun des patients du groupe I n'a présenté des épisodes de H/A, contrairement à six des huit patients du groupe E qui ont présenté plusieurs épisodes en période post-opératoire. Cette différence était statistiquement significative.

Plusieurs doses de morphine en injection épidurale produisent des changements insidieux et imprévisibles du schéma respiratoire. La surveillance électronique est utile afin d'évaluer ceux qui sont à risque de surdosage et possiblement d'arrêt respiratoire.