# Regional Anesthesia and Pain

## Intrathecal + PCA morphine improves analgesia during the first 24 hr after major abdominal surgery compared to PCA alone

*[La morphine intrathécale + la morphine en AAC, comparée à la morphine en AAC seule, améliore l'analgésie pendant les vingt-quatre premières heures suivant une opération abdominale majeure]*

Jean-Michel Devys,* Anne Mora,† Benoît Plaud,* Christian Jayr,‡ Agnès Laplanche,§ Bruno Raynard,¶ Philippe Lasser,# Bertrand Debaene**

**Purpose:** To compare, over a 48-hr follow-up period, the analgesia and side-effects of patient controlled *iv* analgesia (PCA) with morphine alone *vs* combined intrathecal and PCA morphine (IT+PCA) in patients undergoing major abdominal surgery.

**Methods:** Sixty adult patients undergoing abdominal surgery for cancer were randomly allocated to receive preoperative IT (0.3 or 0.4 mg) plus postoperative PCA morphine or postoperative PCA morphine alone. Postoperative analgesia was tested at rest and while coughing on a visual analogue pain scale and morphine consumption was recorded. Patients' satisfaction, arterial oxygen saturation, respiratory rate, episodes of nausea, vomiting and pruritus were also noted.

**Results:** Analgesia at rest and while coughing was significantly better in the IT+PCA morphine group (rest: $P = 0.01$; coughing: $P = 0.005$) on the first postoperative day only. IT+PCA morphine constantly provided adequate analgesia during this period. Morphine consumption was lower in the IT+PCA morphine group during this period also (IT+PCA: 9 (17) *vs* PCA: 40 (26); mg of morphine, mean (SD), $P = 0.0001$). No difference was found in pain relief and morphine consumption between the groups on the second postoperative day. Nausea and vomiting were more frequent with IT+PCA morphine on the first postoperative day. No respiratory depression occurred in either group. Satisfaction was high in both groups.

**Conclusions:** IT+PCA morphine improves patient comfort constantly during the first postoperative day after major abdominal surgery. However, after the first postoperative day, IT+PCA morphine provides no additional benefit.

***Objectif :*** *Comparer, pendant un suivi de 48 h, l'analgésie et les effets secondaires de l'analgésie iv auto-contrôlée (AAC) avec de la morphine seule vs de la morphine en AAC combinée à de la morphine intrathécale (IT+AAC) chez des patients qui subissent une intervention chirurgicale abdominale majeure.*

***Méthode :*** *Soixante patients adultes devant subir une intervention abdominale pour un cancer ont été répartis au hasard et ont reçu de la morphine IT préopératoire (0,3 ou 0,4 mg) plus de la morphine postopératoire en AAC ou seulement de la morphine postopératoire en AAC. L'analgésie postopératoire a été testée au repos et pendant la toux au moyen d'une échelle visuelle analogique. Aussi, on a noté la consommation de morphine, la satisfaction des patients, la saturation de sang en oxygène, le rythme respiratoire, les nausées, les vomissements et le prurit.*

***Résultats :*** *L'analgésie au repos et pendant la toux a été significativement meilleure dans le groupe IT+AAC (repos : P = 0,01 ; toux: P = 0,005) au premier jour postopératoire seulement. La morphine IT+AAC a fourni régulièrement une analgésie adéquate pendant cette période. La consommation de morphine a été plus faible dans le groupe IT+AAC pendant ce même temps (IT+AAC : 9 (17) vs AAC : 40 (26) ; mg de morphine, moyenne (écart type) P = 0,0001). Aucune différence d'analgésie et de consommation de morphine intergroupes n'a été trouvée le deuxième jour postopératoire. Les nausées et les vomissements ont été plus fréquents avec la morphine IT+AAC au premier jour postopératoire. Aucune dépression respiratoire n'a été enregistrée. La satisfaction a été élevée chez les patients des deux groupes.*

From the Departments of Anaesthesiology and Intensive Care,* Adolphe de Rothschild Foundation, Paris; Anaesthesiology,† Henri Duffaux Hospital, Avignon; Anaesthesiology,‡ Biostatistics,§ Intensive Care,¶ and Surgery,# Gustave Roussy Institute, Villejuif; Anaesthesiology and Intensive Care,** Centre Hospitalier Universitaire La Milétrie, Poitiers, France.

*Address correspondence to:* Dr. Jean-Michel Devys, Département d'Anesthésiologie-Réanimation-Urgences, Fondation Adolphe de Rothschild, 25-29 Rue Manin, 75019 Paris, France. Phone: 33-1-48-03-67-76; Fax: 33-1-48-03-65-11; E-mail: jmdevys@fo-rothschild.fr This work should be attributed to the Department of Anaesthesiology, Gustave Roussy Institute, 39 Rue Camille Desmoulins, 94805 Villejuif Cedex, France.

*Accepted for publication September 26, 2002.*
*Revision accepted December 13, 2002.*

***Conclusion :*** *La morphine IT+AAC améliore le confort du patient de façon constante pendant le premier jour postopératoire suivant une opération abdominale majeure. Cependant, par la suite, la morphine IT+AAC ne donne plus d'avantage supplémentaire.*

LOW-DOSE intrathecal morphine (0.1 mg) is an effective, convenient, and simple method for managing short duration postoperative pain after Cesarean section or laparoscopic cholecystectomy.[1,2] More painful operations such as abdominal, spinal or thoracic surgeries require larger doses of morphine to achieve adequate pain relief.[3–5] Moreover, single-shot intrathecal morphine fails to ensure adequate analgesia beyond 24 hr and supplemental *iv* opioid agents may be needed.[5,6] Recently, the combined use of intrathecal morphine and patient-controlled *iv* analgesia (PCA) morphine has been shown to be a valuable approach for analgesia after spinal fusion or thoracic surgeries.[7,8]

Major abdominal surgery results in intense, long lasting pain that is usually controllable with conventional methods of analgesia such as PCA morphine.[9] The role of combined intrathecal + PCA morphine (IT+PCA) for major abdominal surgery in adult patients remains unclear. Therefore, we conducted a prospective randomized study to compare postoperative pain relief and side effects during the first two postoperative days after major abdominal surgery in patients receiving either PCA morphine or IT+PCA morphine.

## Patients and methods

The local Ethics Committee (University Paris XI, Kremlin-Bicêtre, France) approved the study and written informed consent was obtained from each patient. Sixty adult patients (ASA physical status I or II, aged from 18 to 70 yr) scheduled to undergo major abdominal surgery for cancer were randomly allocated by a computer-generated list into two groups to receive either PCA morphine ($n$ = 30) or IT+PCA morphine ($n$ = 30). Exclusion criteria were obesity (body mass index > 30 $kg \cdot m^{-2}$) and any contraindication to spinal puncture.

Premedication consisted of hydroxyzine (1 $mg \cdot kg^{-1}$). Anesthesia was induced with thiopental (5–8 $mg \cdot kg^{-1}$), sufentanil (0.2 $\mu g \cdot kg^{-1}$) and atracurium (0.5 $mg \cdot kg^{-1}$) to facilitate tracheal intubation. Anesthesia was maintained with nitrous oxide/oxygen (0.5/0.5) during mechanical ventilation, isoflurane 1–1.2% end-tidal, atracurium (0.5 $mg \cdot kg^{-1} \cdot hr^{-1}$) and sufentanil boluses (0.1 $\mu g \cdot kg^{-1}$) as required. Tracheal extubation was carried out at the end of the surgery after reversal of the residual neuromuscular block. Nasal oxygen was administered systematically during two hours after extubation. Thereafter nasal oxygen was administered when $SpO_2$ fell below 90%. Nasogastric tube and a bladder catheter were left in place throughout the study.

Before surgery, both groups received instructions on how to use the visual analogue scale (VAS), graded from 0 (no pain) to 100 (worst pain imaginable), and the PCA device. At the end of surgery, 2 g of propacetamol were administered systemically to both groups and every six hours thereafter. When patients of the PCA group complained of pain in the recovery room, they received a titrated dose of morphine (3 mg boluses at ten-minute intervals) to achieve pain relief (VAS at rest < 30 mm). The titrated dose of morphine could not exceed 20 mg. They were then given access to an *iv* PCA pump (APM®, Abbott, Rungis, France) delivering 1 mg morphine boluses with a five-minute lockout interval and no maximum dose was programmed. No background infusion of morphine was used. In the IT+PCA morphine group, preservative-free morphine was injected intrathecally before induction of general anesthesia through a 24-G Sprotte needle inserted in the L3–4 vertebral interspace. Patients received 0.3 mg (3 mL) for submesocolic surgery and 0.4 mg (4 mL) for supra-mesocolic surgery. Patients complaining of pain received no titrated *iv* morphine but were given access to an identically programmed PCA pump.

Every patient was monitored 24 hr in the intensive care unit and in the surgical ward thereafter. Trained nurses evaluated postoperative pain over 48 hr (T0 = extubation time, T48 = end of study period). Measurements were performed at rest and on coughing with a VAS every two hours for 24 hr and every four hours thereafter. Morphine consumption and morphine delivery/demand ratios were also recorded. Sedation scale (awake, sleepy but easily arousable, sleepy and hardly arousable) and adverse effects (nausea, vomiting, pruritus) were evaluated at the same time intervals. Metoclopramide was given in case of vomiting or after two successive episodes of nausea. Satisfaction was quantified at T48 using a 100-mm VAS.

Respiratory depression was assessed with respiratory rate, pulse oximetry and arterial blood gases. Arterial blood gases were sampled while the patient was breathing room air via an arterial catheter two hours after extubation and 12 and 24 hr after the induction of anesthesia. Respiratory rate was recorded every two hours. Oxygen saturation was assessed using a finger probe with a pulse oximeter (N3000, Nellcor Puritan Bennett™, Mallinckrodt Inc., St. Louis, USA) able to store $SpO_2$ in a database. Every five-second

period was averaged by the oximeter and stored in the 36-hr memory set. For offline analysis, the raw $SpO_2$ data were transferred via the RS232 output channel of the monitor using a specially designed program (Score, Nellcor Puritan Bennett™, Mallinckrodt Inc., St. Louis, USA). The oximeter N-3000 used Oxismart technology and rejected $SpO_2$ artefacts. We used the percentage of time spent at a given $SpO_2$, as it has been reported to be an adequate method for assessing hypoxemia.[10] Saturation values were scored as normal ($SpO_2 \geq 95\%$), mild desaturation ($95 > SpO_2 \geq 90\%$) and severe desaturation ($SpO_2 < 90\%$). If the $SpO_2$ dropped below 90% and remained there for two minutes, nasal oxygen was administered to the patient and $SpO_2$ values were not analyzed.

Power calculation for VAS pain scores at rest during the first postoperative day between IT+PCA and PCA patients was based on results from a preliminary study performed at our institution (VAS pain scores at rest IT+PCA: 10 mm, PCA: 30 mm; type 1 error: 5%; type 2 error: 20%; minimal difference not to be overlooked: 20 mm reduced pain score; sample size needed: 20 patients in each group). A Wilcoxon rank sum test was used to compare pain scores during two postoperative periods (T0–T24 and T28–T48) in both groups and satisfaction scores. Patient characteristics, the duration of surgery, sufentanil and morphine consumption, morphine delivery/demand ratio, respiratory rate, arterial blood gas values were compared using Student's t test. The Chi-square test was used to compare sex distribution, the type of surgery, frequency of nausea or vomiting, and frequency of pruritus. Friedman's one-way repeated measure of ANOVA on ranks and multiple comparisons' test and Dunnett's method were used to compare postoperative $SpO_2$ in each group. A $P$ value $< 0.05$ was considered statistically significant.

TABLE I Demographic data of patients scheduled for major abdominal surgery

| | *PCA morphine (n=30)* | *IT+PCA morphine (n = 30)* |
|---|---|---|
| Age (yr) | 52 (11) | 51 (10) |
| Weight (kg) | 65 (9) | 70 (11) |
| Height (cm) | 164 (18) | 167 (8) |
| ASA 1 / 2 / 3 (*n*) | 14 / 15 / 1 | 8 / 21 / 1 |
| Sex (M/F) | 8/22 | 10/20 |
| Duration of surgery (min) | 222 (116) | 193 (85) |
| Time from end of surgery to extubation (min) | 50 (48) | 39 (25) |
| Sufentanil (µg) | 60 (26) | 52 (25) |

PCA = patient-controlled analgesia; IT+PCA = combined intrathecal + PCA. Values are mean (SD). No statistically significant difference.

TABLE II Surgical procedures

| | *PCA morphine (n = 30)* | *IT+PCA morphine (n = 30)* |
|---|---|---|
| *Sub-mesocolic surgeries* | | |
| - Pelvectomy with pelvic and lumbo-aortic lymphadenectomy | 5 | *7* |
| - Hysterectomy with pelvic and lumbo-aortic lymphadenectomy | 10 | 8 |
| - Colectomy | 2 | 0 |
| *Total* | *17* | *15* |
| *Supra-mesocolic surgeries* | | *6* |
| - Hepatectomy | 4 | 2 |
| - Gastrectomy | 3 | 1 |
| - Nephrectomy | 3 | 2 |
| - Splenectomy | 1 | 4 |
| - Laparotomy | 2 | 0 |
| *Total* | *13* | *15* |

PCA = patient-controlled analgesia; IT+PCA = combined intrathecal + PCA. No statistically significant difference between groups.

## Results

Sixty patients were enrolled in the study. No patient was excluded because of uncontrollable pain. The two groups were comparable in terms of age, weight, height, sex distribution, intraoperative sufentanil consumption, time to extubation and for duration or type of surgery (Tables I and II).

Pain scores were significantly lower during the T0–T24 postoperative period in the IT+PCA morphine group than in the PCA morphine group at rest and while coughing (Figures 1 and 2; rest: $P = 0.01$; coughing: $P = 0.005$). No difference was found in the VAS pain score at rest and while coughing during the T28–T48 period (rest: $P = 0.09$; coughing: $P = 0.21$). Seven patients (23%) in the IT+PCA morphine group had a VAS pain score at rest greater than 50 mm before using the PCA pump. Patient satisfaction was not different between groups (IT+PCA: 80 ± 15 *vs* PCA: 72 ± 16, $P = 0.08$).

In the PCA group, 96% of patients used the PCA pump throughout the study. In the IT+PCA morphine group, 20%, 50% and 86% of patients used the PCA pump at T16, T24 and T48 respectively. One IT+PCA patient needed *iv* morphine immediately in the recovery room. Significantly more morphine was used in the PCA morphine group than in the IT+PCA morphine group during the T0–T24 period (Table III). Thereafter there was no difference in the consumption of morphine between the two groups. A

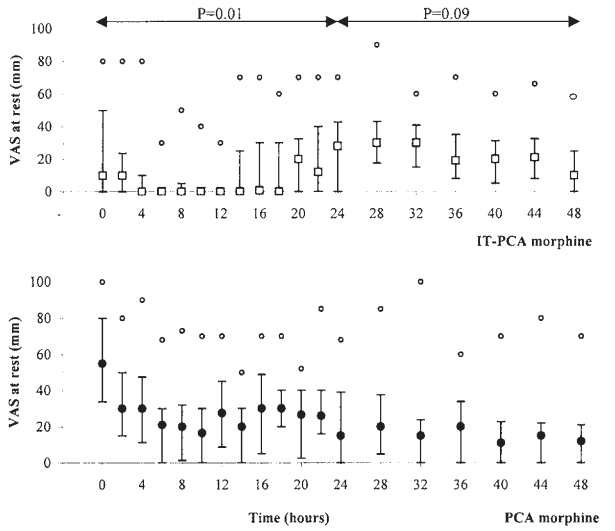


FIGURE 1 Pain relief at rest after major abdominal surgery

Pain scores (VAS) at rest during the first two days after major abdominal surgery in the combined intrathecal+PCA morphine group (IT+PCA morphine; top) and in the PCA (patient-controlled analgesia) morphine group (bottom). Values are median with interquartile range. Open circles represent the highest value. Pain scores are higher in the PCA group than in the IT+PCA morphine group during the first postoperative day (T0–T24) only (T0–T24: $P = 0.01$, T28–T48: $P = 0.09$).

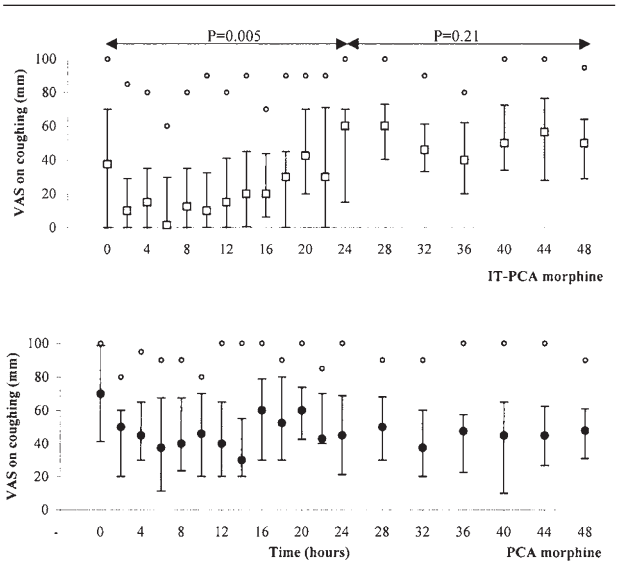


FIGURE 2 Pain relief while coughing after major abdominal surgery

Pain scores (VAS) while coughing during the first two days after major abdominal surgery in the combined intrathecal+PCA morphine group (IT+PCA morphine; top) and in the PCA (patient-controlled analgesia) morphine group (bottom). Values are median with interquartile range. Open circles represent the highest value. Pain scores are higher in the PCA group than in the IT+PCA morphine group the first postoperative day (T0–T24) only (T0–T24: $P = 0.005$, T28–T48: $P = 0.21$).

greater delivery/demand of morphine ratio was observed in the IT+PCA morphine group during the T28–T48 period. During the T0–T24 period, the difference did not reach statistical significance ($P = 0.09$; Table III). There was also no difference in sedation scores (Table IV).

No respiratory rate < 10·min$^{-1}$ was noted in any patient. Ten patients in the IT+PCA morphine group and 15 patients in the PCA morphine group required supplemental nasal oxygen for $SpO_2$ < 90% ($P = 0.19$) and were excluded from $SpO_2$ analysis. There was no difference between the IT+PCA morphine and PCA morphine group for respiratory rate and for the time spent with a $SpO_2 \geq 95\%$ and with $95\% > SpO_2 \geq 90\%$ whatever the period of interest (Figure 3). Arterial blood gases showed a greater $PaCO_2$ in the IT+PCA morphine group at T2 and a lower $PaO_2$ in the PCA morphine group 12 hr after the induction of anesthesia (Table V). Nausea or vomiting was more frequent in the IT+PCA morphine group during the T0–T24 period (IT+PCA morphine group: 53% *vs* PCA morphine group: 23%, $P = 0.016$) but no difference was found during the T28–T48 period (IT+PCA morphine group: 23% *vs* PCA morphine group: 13%, $P = 0.31$). No difference was found for vomiting and severe nausea requiring metoclopramide (IT+PCA morphine group: 23% *vs* PCA morphine group: 16%, $P = 0.12$). No difference was found for pruritus (IT+PCA morphine group: 12% *vs* PCA morphine group: 8%, $P = 0.16$).

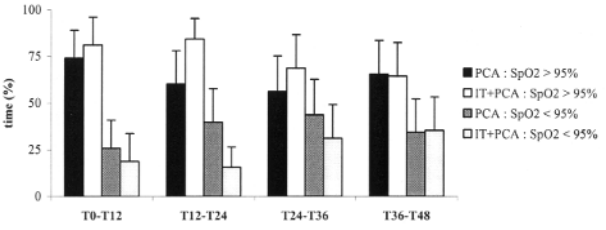


FIGURE 3 Oxygen saturation after major abdominal surgery

Percentage of time spent at different levels of $SpO_2$ for 12-hr postoperative periods (T0–T12, T12–T24, T24–T36 and T36–T48) after major abdominal surgery in PCA (patient-controlled analgesia) morphine group and in combined intrathecal+PCA morphine group (IT+PCA morphine). Values are mean (SD). No statistically significant difference between PCA group and IT+PCA group.

TABLE III Consumption of analgesics after major abdominal surgery

| | *Time period* | *PCA morphine* | *IT+PCA morphine* | *P* |
|---|---|---|---|---|
| Morphine (mg) | T0–T24 | 40 (26) | 9 (17) | 0.0001 |
| | T28–T48 | 26 (21) | 19 (16) | 0.18 |
| Morphine delivery/demand ratio | T0–T24 | 0.69 (0.20) | 0.80 (0.21) | 0.09 |
| | T28–T48 | 0.71 (0.19) | 0.81 (0.14) | 0.03 |

PCA = patient-controlled analgesia; IT+PCA = combined intrathecal + PCA. Values are mean (SD).

TABLE IV Sedation scale after major abdominal surgery

| *Sedation scale* | *PCA morphine (n = 30) Patients (n)* | *IT+PCA morphine (n = 30) Patients (n)* |
|---|---|---|
| Awake | 17 | 19 |
| Sleepy but easily arousable | 10 | 10 |
| Sleepy but hardly arousable | 3 | 1 |

Worst sedation scale score during the first postoperative day after major abdominal surgery for PCA (patient-controlled analgesia) morphine and combined intrathecal + PCA morphine (IT+PCA morphine). No statistically significant difference.

## Discussion

We compared combined IT+PCA morphine and PCA morphine alone in adult patients undergoing major abdominal surgery. As a result, pain relief, assessed with a VAS pain score and according to morphine consumption, was significantly better in the IT+PCA morphine group during the first postoperative day compared to the PCA morphine group. During the second postoperative day, pain relief was not different between groups. Most patients in the IT+PCA morphine group required *iv* morphine during the second postoperative day. Nausea was the main side effect and was more frequent with IT+PCA morphine during the first postoperative day. No respiratory depression was observed with either method of postoperative analgesia during the study.

The higher pain relief with IT+PCA morphine compared to PCA morphine alone after abdominal surgery is not surprising. Similar results have already been published for surgeries such as thoracotomy, spine fusion and Cesarean section.[7,8,11] In the present study, pain relief was better on the first postoperative day only (Figures 1 and 2). In contrast to our results, France *et al.* found a higher pain score and a higher consumption of narcotics in the IT+PCA morphine group than in the PCA group after posterolateral lumbar fusion, during the second postoperative day.[5] This discrepancy may be explained by the high percentage (25%) of patients excluded in the PCA group for uncontrollable pain and by the number of values recorded per patient during these two 48-hr studies (six in the France study *vs* 19 in the present one). In accordance with pain scores on the second postoperative day, the consumption of morphine was not different between the IT+PCA morphine group and the PCA group (Table III). Nevertheless, the PCA delivery/demand ratio of morphine, an indicator of analgesia, was greater in the IT+PCA morphine group (Table III).[12,13]

This prospective randomized study was not double-blinded because of concerns with respiratory depression. Most reported cases of respiratory depression are due to the concomitant use of intrathecal morphine and parenteral morphine.[11,14–16] Synergy between spinal and systemic opioids is well described and most clinicians have advocated against their combined use.[17,18] During a preliminary study, a postoperative respiratory depression occurred from the combination

TABLE V Blood gas exchange after major abdominal surgery

| | *PCA morphine (n = 30)* | *IT-PCA morphine (n = 30)* | *Time* | *P* |
|---|---|---|---|---|
| $PaO_2$ (mmHg) | 75 (18) | 80 (20) | 2 hr after extubation | 0.37 |
| $PaCO_2$ (mmHg) | 45 (6) | 49 (6) | | 0.02 |
| $PaO_2$ (mmHg) | 85 (20) | 86 (11) | 12 hr after induction of anesthesia | 0.7 |
| $PaCO_2$ (mmHg) | 42 (6) | 44 (5) | | 0.17 |
| $PaO_2$ (mmHg) | 76 (16) | 89 (17) | 24 hr after induction of anesthesia | 0.01 |
| $PaCO_2$ (mmHg) | 43 (4) | 41 (6) | | 0.1 |

PCA = patient-controlled analgesia; IT+PCA = combined intrathecal + PCA. Values are mean (SD).

of IT morphine and a low dose of *iv* morphine (1 mg) by PCA. Thus we restricted the use of PCA morphine in the IT+PCA morphine group for documented insufficient pain relief only. Consequently, this lack of free access to PCA morphine was not compatible with a double-blinded procedure.

Intrathecal morphine alone may cause respiratory depression.[15] Clergue *et al.* showed that a dose of spinal morphine (from 2–5 mg) could cause delayed and dose-related respiratory depression after upper abdominal surgery.[19] Respiratory depression may occur even at doses lower than 0.5 mg and the ventilatory response to hypoxemia may be depressed for more than 20 hr after 0.3 mg IT morphine.[20–23] The present study shows no evidence of a greater respiratory risk with IT+PCA morphine than with PCA morphine alone in spite of a higher pain relief with IT+PCA morphine. These results are consistent with those published on the use of spinal morphine for major surgeries.[14] They also suggest that the relative risk of respiratory depression or hypoxemia after IT morphine is fairly low. Slightly greater hypercarbia was found in the IT+PCA morphine group two hours after extubation (Table V). This postoperative hypercarbia could be due to the synergistic effects of IT morphine and intraoperative sufentanil (no difference in sufentanil consumption between groups; Table I) or due to sedation associated with complete analgesia. The combined use of IT and *iv* morphine resulted in respiratory depression with a low respiratory rate and hypoxemia in one patient in the preliminary study. Consequently, we believe these patients should be monitored in an intensive care unit.

Nausea was the most frequent side effect and was more common in the IT+PCA morphine group (55%) during the first postoperative day. The use of intrathecal morphine is often associated with nausea or vomiting and incidences as high as 74% have been reported.[23,24] Evidence of delayed postoperative gastric emptying with a moderate dose (0.6 mg) of intrathecal morphine has been published recently.[25] Nevertheless, patients tended to be more satisfied in the IT+PCA group.

In conclusion, our prospective randomized study showed that combined IT+PCA morphine provides better analgesia than PCA morphine alone after major abdominal surgery. However the short period of highest efficacy (24 hr), a highest rate of nausea and the potential risk of delayed respiratory depression requiring intense postoperative monitoring should be highlighted. The clinical benefit of IT+PCA morphine for major abdominal surgery remains unclear from this study.

## References


1 *Abboud TK, Dror A, Mosaad P, et al.* Mini-dose intrathecal morphine for the relief of post-cesarean section pain: safety, efficacy, and ventilatory responses to carbon dioxide. Anesth Analg 1988; 67: 137–43.

2 *Motamed C, Bouaziz H, Franco D, Benhamou D.* Analgesic effect of low-dose intrathecal morphine and bupivacaine in laparoscopic cholecystectomy. Anaesthesia 2000; 55: 118–24.

3 *Sarma VJ, Bostrom UV.* Intrathecal morphine for the relief of post-hysterectomy pain–a double-blind, dose-response study. Acta Anaesthesiol Scand 1993; 37: 223–7.

4 *Gray JR, Fromme GA, Nauss LA, Wang JK, Ilstrup DM.* Intrathecal morphine for post-thoracotomy pain. Anesth Analg 1986; 65: 873–6.

5 *France JC, Jorgenson SS, Lowe TG, Dwyer AP.* The use of intrathecal morphine for analgesia after posterolateral lumbar fusion. A prospective, double-blind, randomized study. Spine 1997; 22: 2272–7.

6 *Fogarty DJ, Carabine UA, Milligan KR.* Comparison of the analgesic effects of intrathecal clonidine and intrathecal morphine after spinal anaesthesia in patients undergoing total hip replacement. Br J Anaesth 1993; 71: 661–4.

7 *Gall O, Aubineau JV, Berniere J, Desjeux L, Murat I.* Analgesic effect of low-dose intrathecal morphine after spinal fusion in children. Anesthesiology 2001; 94: 447–52.

8 *Mason N, Gondret R, Junca A, Bonnet F.* Intrathecal sufentanil and morphine for post-thoracotomy pain relief. Br J Anaesth 2001; 86: 236–40.

9 *Macintyre PE.* Safety and efficacy of patient-controlled analgesia. Br J Anaesth 2001; 87: 36–46.

10 *Aubry P, Jounieaux V, Rose D, Duran A, Levi-Valensi P.* The $SaO_2$/t diagram as a useful means to express nocturnal hypoxemia. Chest 1989; 96: 1341–5.

11 *Swart M, Sewell J, Thomas D.* Intrathecal morphine for caesarean section: an assessment of pain relief, satisfaction and side-effects. Anaesthesia 1997; 52: 373–81.

12 *McCoy EP, Furness G, Wright PM.* Patient-controlled analgesia with and without background infusion. Analgesia assessed using the demand: delivery ratio. Anaesthesia 1993; 48: 256–65.

13 *Jayr C, Beaussier M, Gustafsson U, et al.* Continuous epidural infusion of ropivacaine for postoperative analgesia after major abdominal surgery: comparative study with i.v. PCA morphine. Br J Anaesth 1998; 81: 887–92.

14 *Gwirtz KH, Young JV, Byers RS, et al.* The safety and efficacy of intrathecal opioid analgesia for acute postoperative pain: seven years' experience with 5969 surgical patients at Indiana University Hospital. Anesth Analg 1999; 88: 599–604.

15 *Rawal N, Arner S, Gustafsson LL, Allvin R.* Present state of extradural and intrathecal opioid analgesia in Sweden. Br J Anaesth 1987; 59: 791–9.
16 *Abouleish E, Rawal N, Rashad MN.* The addition of 0.2 mg subarachnoid morphine to hyperbaric bupivacaine for cesarean delivery: a prospective study of 856 cases. Reg Anesth 1991; 16: 137–40.
17 *Yaksh TL.* Pharmacology and mechanisms of opioid analgesic activity. *In:* Yaksh TL, Lynch CL, Zapol WM, Maze M, Biebuyck JF, Saidman LJ (Eds.). Anesthesia: Biologic Foundations. Philadelphia: Lippincott-Raven; 1997: 921–35.
18 *Ready LB, Oden R, Chadwick HS, et al.* Development of an anesthesiology-based postoperative pain management service. Anesthesiology 1988; 68: 100–6.
19 *Clergue F, Montembault C, Despierres O, Ghesquiere F, Harari A, Viars P.* Respiratory effects of intrathecal morphine after upper abdominal surgery. Anesthesiology 1984; 61: 677–85.
20 *Glass PSA.* Respiratory depression following only 0.4 mg of intrathecal morphine (Letter). Anesthesiology 1984; 60: 256–7.
21 *Bailey PL, Lu JK, Pace NL, et al.* Effects of intrathecal morphine on the ventilatory response to hypoxia. N Engl J Med 2000; 343: 1228–34.
22 *Bailey PL, Rhondeau S, Schafer PG, et al.* Dose-response pharmacology of intrathecal morphine in human volunteers. Anesthesiology 1993; 79: 49–59.
23. *Cousins MJ, Mather LE.* Intrathecal and epidural administration of opioids. Anesthesiology 1984; 61: 276–310.
24 *Pitkanen MT, Niemi L, Tuominen MK, Rosenberg PH.* Effect of tropisetron, a 5-$HT_3$-receptor antagonist, on analgesia and nausea after intrathecal morphine. Br J Anaesth 1993; 71: 681–4.
25 *Lydon AM, Cooke T, Duggan F, Shorten GD.* Delayed postoperative gastric emptying following intrathecal morphine and intrathecal bupivacaine. Can J Anesth 1999; 46: 544–9.