Low-dose sufentanil does not potentiate intrathecal morphine for perioperative analgesia after major colorectal surgery

[Le sufentanil à faible dose ne potentialise pas la morphine intrathécale pour l'analgésie périopératoire après une chirurgie colorectale majeure]

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Purpose: Both intrathecal sufentanil (ITS) and intrathecal morphine (ITM) improve analgesia in obstetrical or cardiac procedures. From a pharmacokinetic standpoint, combining these two opioids may improve perioperative analgesia. We performed a prospective randomized double-blind study to compare the analgesic efficacy of ITM alone *vs* a mixture of a low dose of ITS plus ITM for perioperative pain relief in colorectal surgery.

Methods: Eighty adult patients undergoing colorectal surgery were randomly allocated to receive either 0.4 mg ITM alone or 10 μg ITS plus 0.4 mg ITM before general anesthesia. Intraoperative intravenous sufentanil consumption, postoperative morphine consumption delivered with a patient controlled analgesia device, pain scores, patient satisfaction and adverse effects were recorded for the first 48 hr postoperatively.

Results: No differences were observed between groups with respect to intraoperative sufentanil consumption (39 ± 23 μg in group ITM and 40 ± 25 μg in group ITS plus ITM, $P = 0.85$) and in postoperative morphine consumption in postanesthesia care unit (6 ± 5 mg *vs* 6 ± 5 mg, $P = 0.59$), at 24 hr (26 ± 17 *vs* 24 ± 15 mg, $P = 0.59$) and at 48 hr (47 ± 31 *vs* 44 ± 22 mg, $P = 0.58$). Similarly, no differences were observed in regards to pain relief, patient satisfaction and incidence of adverse effects.

Conclusions: These results do not support the addition of 10 μg ITS to 0.4 mg ITM for colorectal surgery, as low dose sufentanil does not improve intraoperative and postoperative analgesia in this setting.

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Objectif *: Le sufentanil intrathécal (ITS) et la morphine intrathécale (ITM) améliorent tous deux l'analgésie lors de procédures obstétricales ou cardiaques. D'un point de vue pharmacocinétique, la combinaison de ces deux opiacés pourrait améliorer l'analgésie périopératoire. Nous avons mené une étude prospective randomisée en double aveugle afin de comparer l'efficacité analgésique de l'ITM seule vs un mélange d'une faible dose d'ITS ajoutée à l'ITM pour le soulagement de la douleur périopératoire lors de chirurgie colorectale.*

Méthode *: Quatre-vingts patients adultes subissant une chirurgie colorectale ont été randomisés à recevoir soit 0,4 mg ITM seule ou 10 μg ITS plus 0,4 mg ITM avant l'anesthésie générale. La consommation peropératoire de sufentanil intraveineux, la consommation postopératoire de morphine libérée par un appareil d'analgésie contrôlée par le patient, les scores de douleur, la satisfaction des patients ainsi que les effets secondaires ont été enregistrés durant les 48 premières heures postopératoires.*

Résultats *: Aucune différence n'a été observée entre les groupes concernant la consommation peropératoire de sufentanil (39 ± 23 μg groupe ITM et 40 ± 25 μg groupe ITS plus ITM, $P = 0,85$) ou la consommation postopératoire de morphine dans l'unité de soins post-anesthésiques (6 ± 5 mg vs 6 ± 5 mg, $P = 0,59$), à 24 h (26 ± 17 vs 24 ± 15 mg, $P = 0,59$) et à 48 h (47 ± 31 vs 44 ± 22 mg, $P = 0,58$). De même, aucune différence n'a été observée quant au soulagement de la douleur, de la satisfaction des patients et de l'incidence d'effets secondaires.*

Conclusion *: Ces résultats ne soutiennent pas l'addition de 10 μg ITS à 0,4 mg ITM pour la chirurgie colorectale, étant donné que le sufentanil à faible dose n'améliore pas l'analgésie peropératoire et postopératoire dans ce contexte.*

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PERIOPERATIVE pain control with intrathecal (IT) opioid administration has been used successfully in a variety of surgical specialties.[1] Intrathecal morphine (ITM), in particular, is a simple and reliable way of providing effective analgesia after cardiovascular,[2] thoracic,[3] obstetric[4] and orthopedic procedures.[5] In major abdominal surgery, ITM (0.3–0.4 mg) combined with patient controlled analgesia (PCA) improves perioperative analgesia compared to PCA alone during the first 24 hr after surgery.[6,7] Intrathecal morphine has the advantage of providing long-lasting analgesia after a single injection. However, because morphine is a hydrophilic opioid, its peak analgesic effect is delayed (six to seven hours after injection) and its rostral spread carries the risk of late respiratory depression especially at high doses.[1,8]

Sufentanil, on the other hand, is a lipophilic opioid. Therefore, intrathecal sufentanil (ITS) has a very fast onset (five to ten minutes) and is relatively short lived (two to four hours).[1] Its analgesic efficacy at low-doses (2.5–10 μg) combined to a local anesthetic is well documented in obstetrics where it improves analgesia during labour and intraoperative Cesarean delivery.[9–13] In abdominal surgery, sufentanil is usually administered epidurally or intravenously[14,15] and the clinical experience in non-vascular major abdominal surgery with ITS is still limited. A recent study in major abdominal surgery showed that a large dose of ITS (150 μg) was able to blunt the intraoperative stress response and produced effective analgesia, but was associated with prolonged mechanical ventilation.[16]

Combining ITS and ITM may provide the optimal analgesic regimen to cover the intraoperative, the immediate, and the delayed postoperative periods up to 24 hr.[3] This combination of IT opiods has been studied in cardiac,[2,17] abdominal aortic[18] and thoracic[3,19] surgery to shorten the onset of morphine and to reduce ITM dose. However, the doses of ITS used in these studies were relatively high (25–50 μg) to achieve adequate pain relief. In colorectal surgery, lower doses of ITS, similar to those used in obstetrics,[4] might be sufficient to provide adequate intraoperative analgesia. Therefore, we hypothesized that a combination of ITS 10 μg and ITM 0.4 mg compared to ITM 0.4 mg alone, would improve the perioperative pain control of patients undergoing colorectal surgery. We designed and conducted this prospective randomized double-blind study to test our hypothesis.

Methods

The study was approved by our institution Ethics Committee, and written informed consent was obtained from all patients before participation. Eighty adult patients ASA I–III, from 18 to 80 yr of age, scheduled for elective colorectal surgery were included. Patients with neurological disorders, an active infection, receiving opioid therapy for chronic pain, or with abnormal coagulation tests, were excluded. Using a computer generated randomization patients were allocated to one of two groups. Group M, received 0.4 mg preservative-free morphine (2 mL) plus 2 mL 0.9% saline intrathecally; Group SM received 10 μg sufentanil (2 mL) plus 0.4 mg preservative-free morphine (2 mL) intrathecally. The volume of each study solution was 4 mL and was prepared in an adjacent room by an anesthesiologist who took no further part in the study. Treatment allocation was kept concealed in numbered envelopes that were opened consecutively after patient recruitment.

On the day before surgery, all patients were instructed on how to use a PCA device (CADD-Legacy 6300™, Smiths Medical MD, Inc., St. Paul, MN, USA) and a visual analogue scale (VAS) to evaluate pain. The scale consisted of an unmarked 100-mm line (0-mm = no pain and 100-mm = worst pain imaginable). A similar tool was used to assess patient satisfaction.

One hour before surgery, patients were premedicated with oral midazolam 7.5 mg. Upon arrival in the operating room, standard monitoring was instituted (electrocardiogram, non-invasive blood pressure and pulse oximetry) and a peripheral intravenous catheter was inserted. Patients were then placed in the lateral position. Spinal puncture was performed at the L3–L4 or L4–L5 interspace with a 25-G pencil point spinal needle and the study solution was injected into the subarachnoid space. The anesthesiologist who performed the IT injection and managed the patient intraoperatively was not involved in postoperative care or data collection. Both patients and observers were blinded. After the IT injection, general anesthesia was induced with propofol 2–3 $mg \cdot kg^{-1}$ *iv* and sufentanil 0.2 $\mu g \cdot kg^{-1}$ *iv*. Rocuronium 0.6 $mg \cdot kg^{-1}$ *iv* was administered to facilitate endotracheal intubation. Anesthesia was maintained with a mixture of air-oxygen (50%–50%) and desflurane. Heart rate, peripheral oxygen saturation (SaO_2), fractional inspired oxygen concentration, fractional expired carbon dioxide concentration and fractional expired desflurane (FeDES) concentration were controlled continuously. Arterial pressure was measured every five minutes. Surgery started 45 to 60 min after IT injection.

Using a two-step approach, the anesthetic depth was adjusted as required by clinical conditions to maintain heart rate and blood pressure within predefined limits. First, FeDES was increased up to 7%

(low fresh gas flow was maintained) followed by supplemental intravenous sufentanil (10 μg) only if the pulse rate and/or the mean arterial pressure rose 30% above resting values. Rocuronium increments 10–20 mg *iv* were used to facilitate abdominal surgery. At the end of the surgery, patients were awakened, their tracheas were extubated, and they were transferred in the postanesthesia care unit (PACU). Cessation of anesthetic agents was standardized. The time from end of surgery to extubation was recorded.

When sufficiently awake, patients were asked to grade their pain using the VAS. If required (VAS ≥ 30) initial titration of intravenous morphine with boluses of 2 mg was started every five to ten minutes until VAS was below 30. At that point, the intravenous PCA was started and the patient was encouraged to use it when analgesia was deemed necessary. A standard PCA program was used throughout the study period: morphine solution 1 $mg \cdot mL^{-1}$, morphine bolus 1 mg, lock-out five minutes, maximal dose of 40 mg of morphine over four hours, no background infusion. In addition, all patients received intravenous paracetamol every six hours during the first 48 hr. Rescue analgesia (ketorolac 30 mg *iv* every eight hours) was given when the pain score at rest remained ≥ 30 on VAS. Patient satisfaction was assessed at 24 and 48 hr using the VAS.[20] Pain scores at rest and coughing were recorded every six hours during the whole study period. Data recording was done by an independent observer who was unaware of treatment allocation.

At our institution, all patients who receive more than 300 μg of ITM are continuously monitored in PACU for a 24-hr period. If respiratory rate was < 8 $breaths \cdot min^{-1}$ and and/or SaO_2 < 95%, the PCA was stopped and naloxone 40 μg was given intravenously if deemed necessary. Sedation was evaluated in PACU and on the ward using a five-point scale (1 = awake and alert; 2 = sedated, responds to verbal stimulus; 3 = sedated; responds to mild physical stimulus; 4 = sedated, responds to moderate or strong physical stimulus; and 5 = not arousable). Nausea and vomiting were treated with dehydrobenzperidol 0.625 mg *iv*. Adverse effects (respiratory depression, pruritus, nausea and vomiting) were continuously recorded for the first 24 hr and then every six hours up to 48 hr. Foley catheters were routinely used for the first 24 hr. Occurrence of urinary retention was monitored thereafter.

The primary endpoints were the intraoperative consumption of sufentanil, morphine consumption at 24 hr and 48 hr and the pain at rest and on coughing, recorded on the VAS. Secondary endpoints included use of rescue analgesia, patient satisfaction and incidence of adverse effects.

TABLE I Patient characteristics and type and duration of surgery

	Group M (n = 38)	*Group SM (n = 39)*
Analyzed patients (male:female)	38 (21:17)	39 (18:21)
Weight (kg)	70 ± 14	72 ± 13
Height (cm)	170 ± 12	168 ± 10
ASA 1/2/3	6/22/9	9/25/5
Duration of surgery (min)	210 ± 72	196 ± 90
Time to extubation (min)	10 ± 9	10 ± 8
Colorectal surgery		
Anterior resections	13	12
Sigmoidectomy	6	5
Colectomy		
right	8	9
left	10	13

Values are means ± SD, or number of patients. There was no significant difference between the two groups. Group M = intrathecal morphine group; Group SM = intrathecal sufentanil and morphine.

Sample size calculation was performed a priori based on the anticipated intraoperative intravenous sufentanil reduction. Drawing from a previous study which showed a 23% reduction in intraoperative intravenous sufentanil consumption,[3] we estimated that 34 patients per group would be required to detect a significant difference with an α risk set at 5% and a β risk at 20%. Allowing for attrition, we recruited 40 patients per group. Normal distribution of variables was confirmed using the Kolmogorov-Smirnov test. Statistical analysis was performed using unpaired Student's *t* test for comparison of duration of surgery, and consumption of intravenous sufentanil and time from end of surgery to extubation. Visual analogue scale for pain relief and patient satisfaction, as well as postoperative morphine consumption at 24 hr and 48 hr were compared over time with a repeated measure ANOVA. Frequency data were analyzed with the χ^2 or the Fisher exact tests. Data are presented as mean ± SD and ranges. Statistics were performed using a standard statistical package (SPSS 11.0, SPSS Inc., Chicago, IL, USA). A P value < 0.05 was considered significant.

Results

Eighty patients participated in the study (40 per group). Two patients in group M had severe nausea and the PCA device had to be discontinued in the postoperative period. Data derived from these two patients were taken into account for analysis of

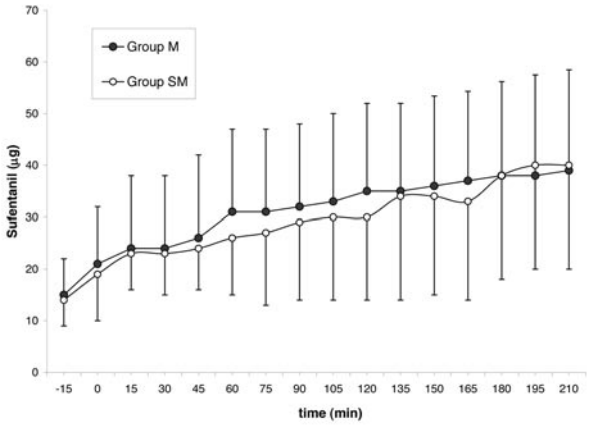

FIGURE 1 Cumulative intravenous sufentanil requirements during surgery. There was no significant difference between groups. Data are mean ± SD. 0 = start of surgery.

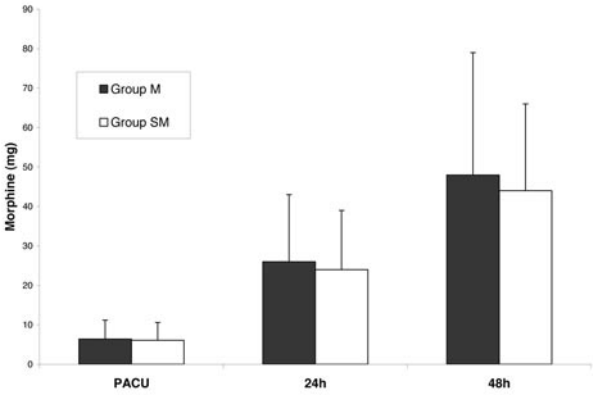

FIGURE 2 Cumulative intravenous morphine consumption in the PACU during the first 24 hr and 48 hr after surgery. Black and white bars represent M and SM groups respectively. There was no significant difference between groups. Data represent mean ± SD. PACU = postanesthesia care unit.

the intraoperative period but were excluded for the postoperative period. In group SM, one patient was excluded because of failure to perform lumbar puncture. A total of 77 patients were therefore prospectively assessed over 48 hr: 38 and 39 in groups M and SM respectively.

Patient characteristics, type and duration of surgery, and time to extubation were similar between the two groups (Table I). Total intraoperative intravenous sufentanil was 39 ± 23 µg in group M and 40 ± 25 µg in group SM (P = 0.85). Figure 1 details the evolution of intraoperative administration of intravenous sufentanil. Overall perioperative morphine consumption is illustrated in Figure 2. Total intravenous morphine titrated in the PACU was 6 ± 5 (0–18) and 6 ± 5 mg (0–20) in group M and SM respectively (P = 0.59). Cumulative morphine consumption during the first 24 hr was 26 ± 17 (1–50) and 24 ± 15 mg (7–50) in group M and SM respectively (P = 0.59). Corresponding doses during the first 48 hr were 47 ± 31 (1–134) and 44 ± 22 mg (9–83) respectively (P = 0.58). In group M, eight patients (21%) received rescue analgesia during the first 24 hr and three (8%) during the following 24 hr compared to 11 (28%) and five (13%) in group SM (P = 0.71).

Visual analogue scale pain scores at rest or on coughing (measured every six hours) and patient satisfaction did not differ at any time point between the groups during the first 48-hr study period (Table II).

No patient had a sedation score at 5. One patient in group M and two patients in group SM had a sedation score of 4 (Table III). The incidence of nausea, vomiting and pruritus were similar between the two groups

TABLE II Visual analogue scale pain scores at rest and with coughing, and patient satisfaction during the first 48 hr after surgery

	Group M (n = 38)	*Group SM (n = 39)*
Pain score in PACU (0-100 mm)	48 ± 30	40 ± 31
Pain score at rest at 24 hr (0-100 mm)	18 ± 12	21 ± 19
Pain score on cough at 24 hr (0-100 mm)	67 ± 27	63 ± 20
Pain score at rest at 48 hr (0-100 mm)	21 ± 9	14 ± 15
Pain score on cough at 48 hr (0-100 mm)	58 ± 21	42 ± 17
Satisfaction at 24 hr (0-100 mm)	81 ± 16	83 ± 11
Satisfaction at 48 hr (0-100 mm)	72 ± 14	81 ± 13

Values are means ± SD, or number of patients. There were no significant differences between the two groups. PACU = postanesthetic care unit; Group M = intrathecal morphine; Group SM = intrathecal sufentanil and morphine.

TABLE III Postoperative adverse effects during the first 48 hr after surgery

	Group M (n = 38)	*Group SM (n = 39)*
PONV	16	14
Pruritus	10	12
Sedation score > 3	1	2

Values are number of patients. There was no significant difference between the two groups. PONV = postoperative nausea and vomiting; Group M = intrathecal morphine; Group SM = intrathecal sufentanil and morphine.

(Table III). No patient required prolonged mechanical ventilation, no respiratory depression occurred and no urinary retention was observed.

Discussion

Our study shows that the combination of ITS 10 μg and ITM 0.4 mg does not provide a substantial clinical benefit compared to ITM 0.4 mg alone when administered in a double-blind randomized design for colorectal surgery. This statement is supported by the absence of significant differences between the two groups in each of the three primary endpoints: intraoperative consumption of intravenous sufentanil, immediate and delayed postoperative intravenous morphine consumption, and pain scores during the first 48 hr after surgery.

Our study investigates the theoretical advantages of combining ITS and ITM over ITM alone for colorectal surgery. Combining the two opioids may provide an optimal analgesic regimen to cover analgesic requirements for the first 24 hr.[1] Previous studies that have demonstrated the benefit of intravenous opioids in abdominal surgery have either compared ITS to intravenous morphine PCA,[16] ITM to intravenous morphine PCA,[7] or a combination of ITS and ITM to intravenous morphine PCA.[18] We decided to conduct this prospective study using doses of ITM and ITS based on experience gained in different surgical settings.[12,21]

Despite these theoretical arguments, our research hypothesis was not confirmed by our results. This study was powered to detect a sparing effect on intraoperative intravenous sufentanil consumption based on Liu's *et al.* study.[3] However, the main difference is that we used a smaller dose of ITS compared to Liu's report (10 *vs* 50 μg). We chose this dose based on two arguments. First, low-doses of IT lipophilic opiods such as fentanyl or sufentanil provide rapid and effective analgesia during labour.[1,13] In addition, low doses of ITS (2.5–10 μg) combined with a local anesthetic hasten the onset of block, and improve intraoperative and postoperative analgesia for two to five hours after Cesarean delivery.[1,13] Our second argument to opt for this ITS dosage was based on a study conducted by Lu *et al.*[22] investigating the dose response of ITS (12.5, 25, or 50 μg) in young adult female volunteers. The authors observed patients' response to lower extremity pain and concluded that doses larger than 12.5 μg did not improve the speed of onset, magnitude, or duration of analgesia but only produced a dose-related increase in side effects (nausea, vomiting and respiratory depression). In addition, higher doses resulted in higher serum sufentanil concentrations, which may further aggravate respiratory depression.

We performed a post-hoc power analysis to test for a possible ß-type error. Assuming that the highest difference that we observed in intraoperative intravenous sufentanil consumption (at 60 min: 30 μg ± 17 μg *vs* 25 μg ± 11 μg in group M and SM respectively) would persist, 124 patients per group would be needed to demonstrate a significant difference. Although significant, such an opioid sparing effect (i.e., 5 μg of intravenous sufentanil) would be of small magnitude and thus of limited clinical relevance.

It is possible, however that we opted for an insufficient dose of ITS. Nociceptive stimuli during colorectal surgery may involve different pain pathways including neuro-humoral and immunological responses, sympathetic and pituitary-adreno-cortical axis activation which may differ from those observed in obstetric, orthopedic or vascular surgery.[23] In fact, large doses of ITS (150 μg) have been shown to partially blunt the stress response and to reduce postoperative cumulative intravenous morphine consumption.[16] However, there are controversies about the neurotoxicity of large doses of ITS. Rawal *et al.*,[24] have shown in a sheep model that doses of 150 to 240 μg ITS were associated with histopathological changes. On the other hand, Sabbe *et al.*,[25] showed no evidence of neurotoxicity [cerebrospinal fluid (CSF) and histopathologic analyses] after several daily injections of 5, 25, or 50 μg ITS in a dog model. It is therefore reasonable to think that ITS doses should not exceed 50 μg. One can argue that 10 μg ITS was insufficient in our study, but the combination of 50 μg ITS and 0.5 mg ITM were not superior to ITM alone in thoracic surgery, even though this study was probably underpowered (ten patients per group).[3] Again, it is possible that a ceiling effect similar to the one observed in volunteers[22] or in the obstetrical setting[21] may also exist for ITS. A properly powered dose-response study investigating ITS combinations to ITM in colorectal surgery could answer this question. However, according to our results the expected clinical benefits are likely to be minor.

Another explanation can be advanced to explain our negative results. Lipophilic properties of sufentanil result in a rapid clearance from the CSF towards plasma after IT administration.[26] Hansdottir *et al.*,[27] administered 15 μg of ITS and observed that the peak plasma concentration of sufentanil appeared after 39 min and that the mean residence time in CSF was 55 min. The rapid pharmacokinetics of sufentanil explain its rapid onset of action and short-lasting effects. As in our study the beginning of surgery started 30 to 45 min after the IT injection, it is possible that the CSF sufentanil concentration was insufficient to provide

analgesia at the start of surgery. It is therefore not surprising that the analgesic effect of ITS did not last into the postoperative period.

Despite the lack of effectiveness of ITS, its use in association with ITM did not increase the incidence of adverse effects. In particular, we did not observe significantly delayed extubation times. This may be related to a precise stepwise protocol, avoiding any overdosage of intravenous sufentanil, and our routine practice to extubate all patients in the operating room. Such institutional practices may greatly influence extubation times as illustrated by Devys *et al.*'s[7] results. Their study was conducted in France where patients are routinely extubated in the PACU and even though they used doses of ITM similar to ours, mean times to extubation were 50 min in the control group (no ITM) and 39 min in the group receiving ITM.

Although we did not observe any respiratory depression, we stress the fact that 400 μg of ITM may be excessive at institutions unable to provide overnight monitoring of patients. This dose is higher than the current recommendation for common surgical procedures.[5,28,29] However, in contrast to orthopedic or obstetrical procedures, the optimal dose of ITM for major abdominal surgery has not yet been determined, although others have successfully used ITM doses in the range that we have studied.[6,7] It is possible that had we used a lower dose of ITM, then the analgesic benefit of ITS may have been unveiled. Although this combination may appear attractive at institutions unable to closely monitor patients overnight, this hypothesis needs to be formally tested.

We conclude that in spite of the rationale for combining a lipophilic with an hydrophilic opioid, there is no evidence that a low dose ITS added to ITM shortens onset of morphine and improves perioperative analgesia in colorectal surgery. As discussed above, the duration of analgesia may be enhanced with larger doses of ITS. However, since previous studies have suggested that higher dosages of ITS may be neurotoxic and that a ceiling effect may exist, the expected benefits of such IT opioid combinations compared to morphine alone are likely to be minor and probably not clinically relevant in this setting. Therefore, we believe that further studies investigating the effectiveness of higher ITS dosages combined with ITM in colorectal surgery may be designed in a dose-response pattern within non-toxic ITS dosage ranges.

References

1 *Rathmell JP, Lair TR, Nauman B.* The role of intrathecal drugs in the treatment of acute pain. Anesth Analg 2005; 101: S30–43.

2 *Bettex DA, Schmidlin D, Chassot PG, Schmid ER.* Intrathecal sufentanil-morphine shortens the duration of intubation and improves analgesia in fast-track cardiac surgery. Can J Anesth 2002; 49: 711–7.

3 *Liu N, Kuhlman G, Dalibon N, Moutafis M, Levron JC, Fischler M.* A randomized, double-blinded comparison of intrathecal morphine, sufentanil and their combination versus IV morphine patient-controlled analgesia for postthoracotomy pain. Anesth Analg 2001; 92: 31–6.

4 *Dahl JB, Jeppesen IS, Jorgensen H, Wettrslev J, Moiniche S.* Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia: a qualitative and quantitative systematic review of randomized controlled trials. Anesthesiology 1999; 91: 1919–27.

5 *Rathmell JP, Pino CA, Taylor R, Patrin T, Viani BA.* Intrathecal morphine for postoperative analgesia: a randomized, controlled, dose-ranging study after hip and knee arthroplasty. Anesth Analg 2003; 97: 1452–7.

6 *Beaussier M, Weickmans H, Parc Y, et al.* Postoperative analgesia and recovery course after major colorectal surgery in elderly patients: a randomized comparison between intrathecal morphine and intravenous PCA morphine. Reg Anesth Pain Med 2006; 31: 531–8.

7 *Devys JM, Mora A, Plaud B, et al.* Intrathecal + PCA morphine improves analgesia during the first 24 hr after major abdominal surgery compared to PCA alone. Can J Anesth 2003; 50: 355–61.

8 *Bailey PL, Rhondeau S, Schafer PG, et al.* Dose-response pharmacology of intrathecal morphine in human volunteers. Anesthesiology 1993; 79: 49–59; discussion 25A.

9 *Camann WR, Denney RA, Holby ED, Datta S.* A comparison of intrathecal, epidural, and intravenous sufentanil for labor analgesia. Anesthesiology 1992; 77: 884–7.

10 *Campbell DC, Camann WR, Datta S.* The addition of bupivacaine to intrathecal sufentanil for labor analgesia. Anesth Analg 1995; 81: 305–9.

11 *Dahlgren G, Hultstrand C, Jakobsson J, Norman M, Eriksson EW, Martin H.* Intrathecal sufentanil, fentanyl, or placebo added to bupivacaine for cesarean section. Anesth Analg 1997; 85: 1288–93.

12 *Karaman S, Kocabas S, Uyar M, Hayzaran S, Firat V.* The effects of sufentanil or morphine added to hyperbaric bupivacaine in spinal anaesthesia for caesarean section. Eur J Anaesthesiol 2006; 23: 285–91.

13 *Hamber EA, Viscomi CM.* Intrathecal lipophilic opioids as adjuncts to surgical spinal anesthesia. Reg Anesth Pain Med 1999; 24: 255–63.

14 *Broekema AA, Kuizenga K, Hennis PJ.* Does epidural

sufentanil provide effective analgesia per- and postoperatively for abdominal aortic surgery? Acta Anaesthesiol Scand 1996; 40: 20–5.
15 *De Kock M, Famenne F, Deckers G, Scholtes JL.* Epidural clonidine or sufentanil for intraoperative and postoperative analgesia. Anesth Analg 1995; 81: 1154–62.
16 *Borgdorff PJ, Ionescu TI, Houweling PL, Knape JT.* Large-dose intrathecal sufentanil prevents the hormonal stress response during major abdominal surgery: a comparison with intravenous sufentanil in a prospective randomized trial. Anesth Analg 2004; 99: 1114–20.
17 *Swenson JD, Hullander RM, Wingler K, Leivers D.* Early extubation after cardiac surgery using combined intrathecal sufentanil and morphine. J Cardiothorac Vasc Anesth 1994; 8: 509–14.
18 *Fleron MH, Weiskopf RB, Bertrand M, et al.* A comparison of intrathecal opioid and intravenous analgesia for the incidence of cardiovascular, respiratory, and renal complications after abdominal aortic surgery. Anesth Analg 2003; 97: 2–12.
19 *Mason N, Gondret R, Junca A, Bonnet F.* Intrathecal sufentanil and morphine for post-thoracotomy pain relief. Br J Anaesth 2001; 86: 236–40.
20 *Hudcova J, McNicol E, Quah C, Lau J, Carr DB.* Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. Cochrane Database Syst Rev 2006: CD003348.
21 *Pan MH, Wei TT, Shieh BS.* Comparative analgesic enhancement of alfentanil, fentanyl, and sufentanil to spinal tetracaine anesthesia for cesarean delivery. Acta Anaesthesiol Sin 1994; 32: 171–6.
22 *Lu JK, Schafer PG, Gardner TL, et al.* The dose-response pharmacology of intrathecal sufentanil in female volunteers. Anesth Analg 1997; 85: 372–9.
23 *Benarroch EE.* Pain-autonomic interactions. Neurol Sci 2006; 27 Suppl 2: S130–3.
24 *Rawal N, Nuutinen L, Raj PP, et al.* Behavioral and histopathologic effects following intrathecal administration of butorphanol, sufentanil, and nalbuphine in sheep. Anesthesiology 1991; 75: 1025–34.
25 *Sabbe MB, Grafe MR, Mjanger E, Tiseo PJ, Hill HF, Yaksh TL.* Spinal delivery of sufentanil, alfentanil, and morphine in dogs. Physiologic and toxicologic investigations. Anesthesiology 1994; 81: 899–920.
26 *Ummenhofer WC, Arends RH, Shen DD, Bernards CM.* Comparative spinal distribution and clearance kinetics of intrathecally administered morphine, fentanyl, alfentanil, and sufentanil. Anesthesiology 2000; 92: 739–53.
27 *Hansdottir V, Hedner T, Woestenborghs R, Nordberg G.* The CSF and plasma pharmacokinetics of sufentanil after intrathecal administration. Anesthesiology 1991; 74: 264–9.
28 *Palmer CM, Emerson S, Volgoropolous D, Alves D.* Dose-response relationship of intrathecal morphine for postcesarean analgesia. Anesthesiology 1999; 90: 437–44.
29 *Murphy PM, Stack D, Kinirons B, Laffey JG.* Optimizing the dose of intrathecal morphine in older patients undergoing hip arthroplasty. Anesth Analg 2003; 97: 1709–15.

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