Intrathecal sufentanil and morphine for post-thoracotomy pain relief†

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In this double-blind randomized study we compared a group of 15 patients undergoing thoracotomy who received a spinal injection of sufentanil 20 μg combined with morphine (200 μg) after induction of general anaesthesia with a control group of the same size. Post-operative pain was rated on a visual analogue scale (VAS) and a verbal rating scale at rest and with a VAS on coughing. In the recovery room, patients received titrated i.v. morphine until the VAS score was <30, and were followed by patient-controlled analgesia (PCA) for 72 h. The intrathecal sufentanil and morphine group had a lower intra-operative requirement for i.v. sufentanil and needed less i.v. morphine for titration in the recovery room. I.v. PCA morphine consumption and pain scores were lower in the active group than in the control group during the first 24 h. There were no differences after this time. Spirometric data (peak expiratory flow, forced vital capacity and forced expiratory volume in 1 s) were similar in the two groups. We conclude that the combination of intrathecal sufentanil and morphine produces analgesia of rapid onset and with a duration of 24 h.

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Post-thoracotomy pain is one of the most severe types of post-operative pain, and its management is a considerable challenge. Several analgesic techniques, including intercostal, paravertebral, interpleural and epidural blocks with local anaesthetics and opioids, have been used to provide pain relief after thoracotomy.[1] All these techniques have limitations, including short duration of action with intercostal nerve blocks, lack of efficacy with interpleural block and side-effects such as respiratory depression, urinary retention, and nausea and vomiting with epidural opioid analgesia. Although the administration of epidural local anaesthetics and opioids after thoracic surgery is considered the cornerstone of analgesic management, experience with intrathecal administration of opioids is limited.[1]

The intrathecal administration of morphine in post-operative patients was first reported in 1979.[2] Although in the following years this technique was shown to provide effective analgesia of long duration in the post-operative period, its use has been restricted compared with epidural analgesia, because of the alleged higher incidence of side-effects with intrathecal opioids.[3] Nevertheless, intrathecal opioid administration has been investigated more recently in the context of major surgery, especially cardiac.[4–10]

The onset and duration of action of intrathecal and epidural opioids depend on their lipid solubility.[11] Intrathecal morphine has a long duration of action but a slow onset of action. On the contrary, lipid-soluble opioids such as fentanyl and sufentanil have a rapid onset but shorter duration of action. Combining epidural morphine and sufentanil may produce analgesia of rapid onset and long duration.[12 13] Intrathecal administration of both drugs may produce a similar profile and therefore we performed a study of this technique in patients after thoracic surgery.

Patients and methods

Thirty ASA I–III patients with lung cancer scheduled for lung resection by a posterolateral thoracotomy were included in this double-blind, randomized study, after written informed consent had been obtained and ethics committee approval had been given. Patients more than 80 yr or less than 18 yr old were excluded, as well as those with disorders of haemostasis or thoracic spine abnormalities.

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Patients were allocated to a control group or a group given intrathecal morphine and sufentanil (SM group). Randomization was performed on the morning of surgery. In both groups, premedication consisted of flunitrazepam 1 mg. Anaesthesia was induced with propofol 2.5 mg kg^{-1} and sufentanil 0.5 μg kg^{-1}. Tracheal intubation was facilitated by atracurium 0.5 mg kg^{-1}. Anaesthesia was maintained with isoflurane (end-tidal concentration 0.8–1.5%). Any increase in arterial pressure (systolic arterial pressure >130 mm Hg or >150% of the preinduction value) and tachycardia (>120 min^{-1} or >150% of the preinduction value) led to the administration of sufentanil 0.5 μg kg^{-1}. A pulsed warm-air device (Bair Hugger®, Augustine Medical Inc., Eden Prairie, MN, USA) was applied to the lower body to maintain body temperature during surgery. Indicators for extubation were recovery from anaesthesia, spontaneous breathing (end-tidal carbon dioxide ⩽42 mm Hg), a stable haemodynamic condition and normothermia.

In the SM group, intrathecal administration of opioids was performed before surgical incision through a 24 G Sprotte needle inserted in the L3–4 or L4–5 vertebral interspace, in the lateral position. Patients received 4 ml of a solution containing sufentanil 20 μg and morphine 200 μg. In the control group, patients had the skin prepared with antiseptic and covered with an adhesive dressing in an identical manner to the intrathecal group.

When patients complained of pain in the recovery room, they received a titrated dose of morphine (2 mg bolus at 5 min intervals) until the visual analogue scale (VAS) score was <30. They were then given access to an i.v. patient-controlled analgesia (PCA) pump (APM®, Abbott, Rungis, France) delivering 1 mg morphine bolus doses with a 7 min lockout interval (maximum dose 30 mg 4-hourly). Morphine was diluted to 1 mg ml^{-1} in a solution also containing droperidol 5 mg in 50 ml. PCA was maintained for 72 h. After 3 days, analgesia was maintained by subcutaneous administration of morphine.

Post-operative pain was evaluated by an anaesthetist blinded to treatment groups, using a VAS graded from 0 (no pain) to 100 (worst pain imaginable) and a verbal rating scale (VRS) (0=no pain; 1=mild; 2=moderate; 3=severe; 4=unbearable). Measurements were performed at rest and on coughing with the VAS, and at rest only with the VRS, 1, 2, 4, 6, 12, 18, 24, 36, 48 and 72 h after arrival in the recovery room.

Side-effects, including respiratory depression (respiratory rate <8 b.p.m.), sedation (not rousable except by persisting verbal or tactile stimulation), urinary retention (requiring transient bladder catheterization), nausea, vomiting and pruritus, were recorded at the same intervals.

Spirometry was performed for the determination of forced expiratory volume in 1 s (FEV_1), peak expiratory flow rate (PEFR) and forced vital capacity (FVC), before surgery and at 6, 24, 48 and 72 h after surgery.

The main goal of the study was to demonstrate a 50% difference in i.v. morphine consumption between the two groups. Assuming that mean (SD) morphine consumption would be about 50 (25) mg per 24 h, we calculated that a sample of 20 patients would be enough to detect such a difference with a type I error of 0.05 and a type II error of 0.10. Statistical analysis was by unpaired Student's *t*-test for comparison of patient characteristics, duration of surgery, i.v. sufentanil and morphine doses and extubation delay. Two-way analysis of variance and the Scheffé F-test were used to compare VAS scores. The Mann–Witney rank sum test was used to analyse morphine consumption and VRS scores. $P<0.05$ was considered significant.

Results

Patient characteristics, duration of surgery and extubation delay were similar in the two groups (Table 1). The mean dose of i.v. sufentanil during surgery was significantly greater in the control group (Table 2). The mean titrated dose of i.v. morphine in the recovery room was also significantly greater in the control group. The time to the first administration of PCA was similar in the two groups. Over the first 24 post-operative hours, i.v. morphine consumption was significantly lower in the SM group but it was similar in the two groups between 24 and 72 h (Table 2 and Fig. 1). Cumulative i.v. morphine consumption was greater in the control group from 8 to 24 h (Fig. 1).

In the recovery room, most of the patients were unable to cough at 15 and 30 min. VAS scores at rest and on coughing were significantly higher in the control group from 1 to 24 h (Figs 2 and 3). VRS scores were also significantly higher from 1 to 24 h (Table 3). Values of PEFR, FEV_1 and FVC were not significantly different between the groups but post-

Table 1 Patient characteristics, duration of surgery and extubation delay. Data are mean (SD). No significant differences

	Control group	SM group
Sex (M/F)	9/6	12/3
Age (yr)	63 (31–85)	56 (42–71)
Weight (kg)	67 (19)	72 (11)
Height (cm)	169 (10)	174 (7)
Duration of surgery (min)	89 (31)	96 (31)
Extubation delay (min)	28 (17)	24 (22)

Table 2 Mean (SD) i.v. opioid consumption.*$P<0.05$

	Control group	SM group
Intraoperative i.v. sufentanil (μg)	34 (11)*	24 (10)
I.v. morphine in recovery (mg)	7.6 (3.6)*	3.4 (4.3)
Time to first PCA i.v. bolus (min)	118 (27)	150 (98)
0–24 h PCA morphine consumption (mg)	36 (15)*	18 (15)
24–72 h PCA morphine consumption (mg)	31 (23)	27 (27)

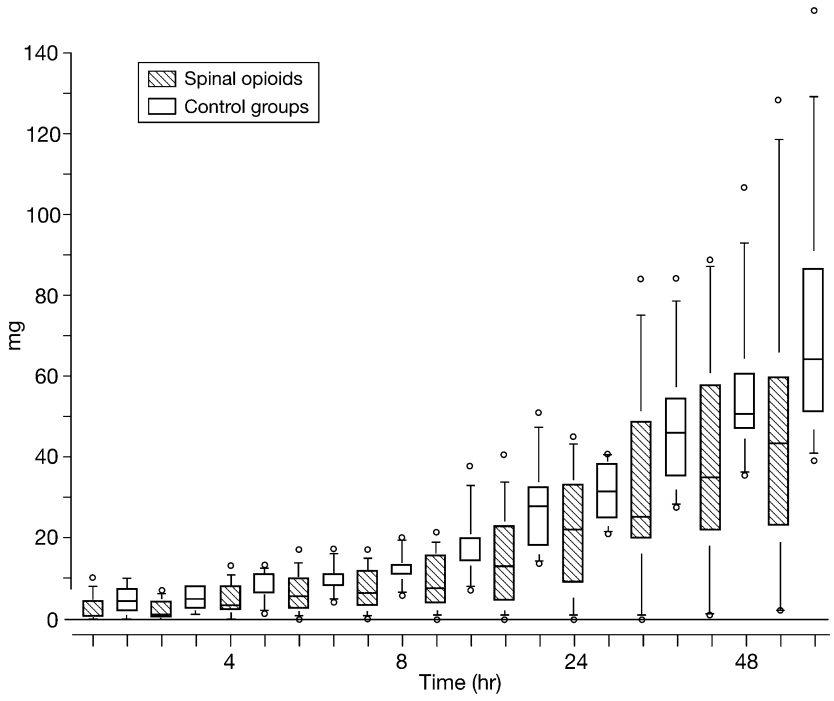

Fig 1 Distribution of cumulative morphine i.v. dose. Values are presented as box plots (25th–75th percentiles) with bars showing the median and the 10th and 90th percentiles and open circles the extremes. At each time interval, the first box represents patients receiving intrathecal sufentanil + morphine (opioid group) and the second box the control group. Values for the control group are significantly greater than those for the opioid (sufentanil + morphine) group from 8 to 24 h (P<0.05).

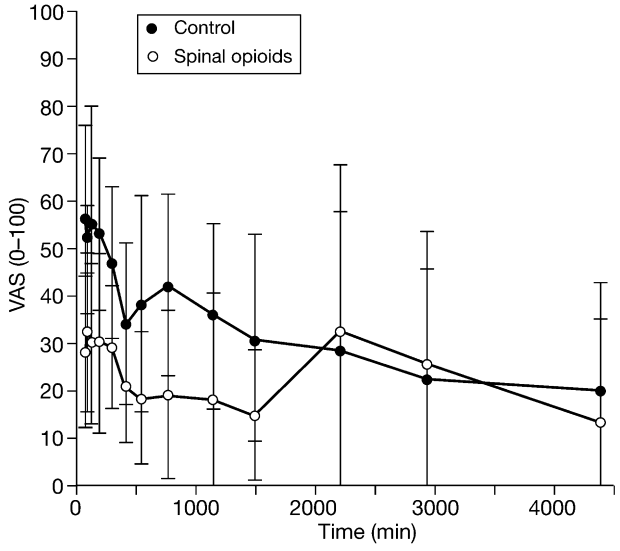

Fig 2 Mean (SD) changes in VAS scores at rest. P values for intergroup comparisons were <0.05 between 60 and 1440 min (1 and 24 h).

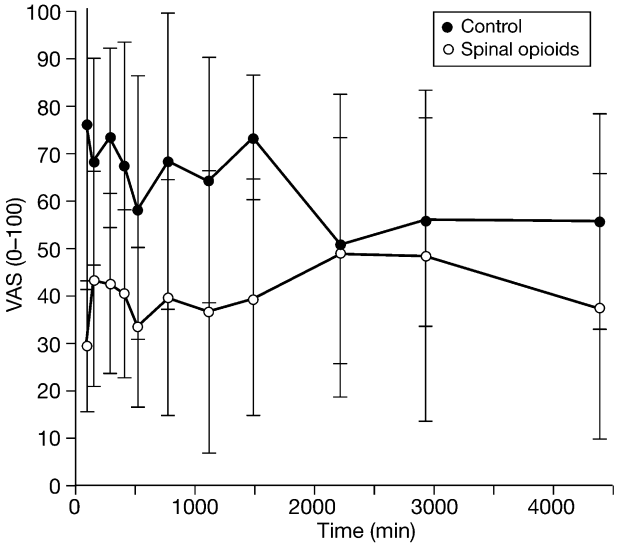

Fig 3 Mean (SD) changes in VAS scores on coughing. P values for intergroup comparisons were <0.05 between 60 and 1440 min (1 and 24 h).

operative values decreased significantly in both groups compared with pre-operative values (Fig. 4).

Six patients in the SM group and four in the control group suffered urinary retention (not significant), no patient received naloxone and three patients in each group complained of nausea and vomiting.

Discussion

This study demonstrated that intrathecal administration of a combination of sufentanil and morphine after thoracotomy resulted in a 50% reduction in the i.v. morphine requirement over the first 24 post-operative hours, while VAS and VRS

scores at rest and on coughing were also lower during the same period. After 24 h, i.v. morphine consumption and pain scores were similar in the two groups.

Only three previous double-blind, randomized studies have assessed the use of intrathecal opioids for post-thoracotomy analgesia, despite the simplicity of the technique.[4 5 7] One of these[5] demonstrated the advantages of a combined intercostal block; the others demonstrated that VAS pain scores and i.v. morphine requirements were less in patients receiving either intrathecal morphine[4] or fentanyl.[7] Most of the studies concerning the administration of intrathecal opioids in thoracic or cardiac surgery focused on the first 24 post-operative hours and evaluated pain at rest.[4 5 7 10 14 15] A decrease in rescue i.v. morphine is reported consistently over this period. Chaney and colleagues, who extended the study period to 48 h, found that morphine consumption was reduced only during the first 24 h.[9] In only one study were VAS scores at rest lower over a 30-h period in a treated group that received intrathecal morphine 500 μg.[16]

Table 3 Verbal rating scores at rest. Values are median (extremes).*$P<0.05$

Time	Control group	SM group
15 min	2 (1–3)	2 (0–3)
30 min	2 (0–3)	2 (0–3)
1 h	2 (1–3)	1 (0–3)
2 h	2 (1–3)	2 (0–3)
4 h	2 (1–3)*	1 (0–2)
6 h	2 (1–3)*	1 (0–2)
8 h	2 (0–2)*	1 (0–2)
12 h	2 (0–3)*	0 (0–2)
18 h	1 (0–2)*	0 (0–2)
24 h	1 (1–3)*	0 (0–2)
36 h	1 (0–2)	1 (0–3)
48 h	1 (0–2)	1 (0–3)
72 h	0 (0–3)	0 (0–2)

Morphine was administered at the lumbar level and might achieve effective analgesic CSF concentrations at the thoracic level only after significant cephalad movement of the lumbar CSF. Thus intrathecal morphine might require several hours to produce adequate pain control. To decrease the delay in the action of morphine, we combined it with sufentanil. Although we did not compare the SM group with a group of patients receiving only morphine, the comparison with the control group demonstrates that the combination of morphine and sufentanil is immediately effective in the post-operative period. Indeed, patients in the treated group required less i.v. morphine in recovery despite the greater dose of i.v. sufentanil administered during surgery. Previous data supporting this finding have shown the superiority of intrathecal over the i.v. and epidural routes of sufentanil administration.[17] However, the rapid clearance of sufentanil from the CSF[18] does not guarantee analgesia of long duration, which is better ensured by intrathecal morphine.

The duration of action of the combination of intrathecal morphine and sufentanil was, nevertheless, limited to 24 h. A larger dose of morphine may increase duration but would increase the incidence of side-effects, especially respiratory depression.

Pain at rest was well controlled in patients in the group receiving spinal opioids. On the contrary, some patients in this group and most of the patients in the i.v. morphine (control) group experienced severe pain on coughing during the first 24 h. Despite clear recommendations, only a minority of other studies have measured dynamic pain after thoracic surgery. Perttunen and colleagues reported pain intensity on coughing similar to the present results in patients treated by epidural, paravertebral and intercostal

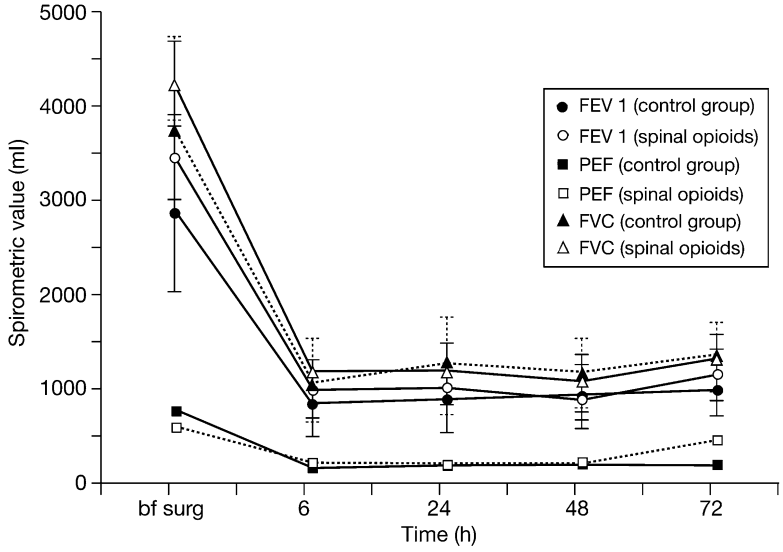

Fig 4 Mean (SD) changes in forced vital capacity (FVC), forced expiratory volume in 1 s (FEV 1) and peak expiratory flow (PEF). Values are not significantly different between the groups. Post-operative values are significantly lower than pre-operative values ($P<0.05$).

nerve blocks,[19] and Guinard and colleagues also described high VAS scores on coughing in patients given i.v. or lumbar or thoracic epidural fentanyl.[20] From these results, it can be concluded that even analgesic techniques considered as being very effective may fail to give complete pain control after thoracic surgery.

Supplementary i.v. morphine was still required in the SM group, indicating that intrathecal opioid administration did not give complete analgesia. Therefore, we consider intrathecal administration to be the core of a multimodal analgesic approach, including parenteral administration of other analgesic agents—an approach recommended by others.[21]

Intrathecal morphine and sufentanil did not delay extubation in the present study. This is at variance with studies concerning coronary artery bypass grafting (CABG).[8 9] In one study, the authors administered a large dose of morphine (4 mg) but patients received controlled ventilation for more than 12 h.[8] In the other study, the same authors reported that intrathecal morphine 10 μg kg^{-1} delayed tracheal extubation significantly.[9] This dose was higher than that given in the present study, and the CABG patients also received large i.v. doses of fentanyl during surgery. Shroff and colleagues administered intrathecal morphine 10 μg kg^{-1} combined with intrathecal fentanyl 25 μg, but they gave i.v. opioid on demand, during CABG.[10] They demonstrated that extubation occurred earlier in the intrathecal group than in the control group. After intrathecal administration of sufentanil 50 μg and morphine 500 μg, 'early' extubation was also possible[6] but, after CABG surgery, whatever the dose of opioid administered, extubation never occurred before several hours of controlled ventilation, making any comparison with thoracic surgery for lung resection rather difficult.

This study confirms the lack of effect of intrathecal opioids on spirometric variables indicative of post-operative pulmonary function, despite better control of post-operative pain.[22] Occasionally, others have demonstrated a marginal correction in the post-operative decrease in respiratory performance.[7 14] Data from most studies are in agreement with those of the present study, even if it can be demonstrated that effective post-operative analgesia decreases post-operative pulmonary morbidity.[22] Urinary retention was the most worrisome complication in our study, confirming the reports of others.[23]

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