Addition of meperidine to bupivacaine for spinal anaesthesia for Caesarean section†

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Background. In a prospective, randomized, double-blind, placebo-controlled trial, we investigated the effect of adding meperidine 10 mg to intrathecal bupivacaine on the duration of early postoperative analgesia in 40 patients having elective Caesarean section under spinal anaesthesia.

Methods. Patients received intrathecal injection of 0.5% hyperbaric bupivacaine 2.0 ml plus either normal saline 0.2 ml (saline group) or 5% meperidine 0.2 ml (meperidine group). After operation, all patients were given i.v. patient-controlled analgesia using morphine.

Results. The duration of effective analgesia, defined as the time from intrathecal injection to first patient-controlled analgesia demand, was greater in the meperidine group (mean 234 min, 95% confidence interval 200–269 min) compared with the saline group (mean 125 min, 95% confidence interval 111–138 min; $P<0.001$). The 24 h morphine requirement was similar in the two groups. The meperidine group had a greater incidence of intraoperative nausea or vomiting compared with the saline group (11 *vs* 3; $P=0.02$).

Conclusion. Addition of meperidine 10 mg to intrathecal bupivacaine for Caesarean section is associated with prolonged postoperative analgesia but with greater intraoperative nausea and vomiting.

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Although a local anaesthetic solution may be used alone for spinal anaesthesia, opioids are commonly added. When the lipophilic opioids fentanyl and sufentanil were added to local anaesthetic, early postoperative analgesia was prolonged compared with local anaesthetic alone.[1–3] In these studies, the reported times to first postoperative analgesic ranged from 4 to 13 h.[4] For morphine, which is more hydrophilic, postoperative analgesia may extend up to 24 h.[5–7] Meperidine is an opioid of intermediate lipid solubility and is unique in having significant local anaesthetic properties.[8] It has been used as the sole agent for spinal anaesthesia for Caesarean section.[9–11] However, few data are available on the effect of adding meperidine to local anaesthetics. Therefore, the purpose of this study was to investigate the effect of adding meperidine to hyperbaric bupivacaine in patients having elective Caesarean section under spinal anaesthesia. The primary outcome measurement was the duration of early postoperative analgesia. Secondary outcomes included cumulative analgesic requirement in the first 24 h and intraoperative side effects.

Methods

After approval from the Clinical Research Ethics Committees of the Chinese University of Hong Kong and the United Christian Hospital, we recruited 40 ASA class I or II patients who were scheduled for elective Caesarean section under spinal anaesthesia in this randomized double-blind study. Patients were eligible for recruitment if they had singleton pregnancies of more than 36 weeks gestation.

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Table 1 Maternal and neonatal data (mean (SD) or number)

	Saline group	Meperidine group	*P*
Maternal characteristics			
Age (yr)	33 (6)	33 (5)	0.83
Body mass index	27.7 (3.9)	26.8 (3.7)	0.43
Parity			
0	4	2	
1	16	11	
>1	0	7	0.014
Neonatal characteristics			
Weight (kg)	3.2 (0.5)	3.2 (0.5)	0.97
Umbilical venous blood gases			
pH	7.31 (0.06)	7.33 (0.03)	0.29
P_{O_2} (kPa)	3.87 (1.09)	3.94 (0.91)	0.83
Umbilical arterial blood gases			
pH	7.26 (0.07)	7.26 (0.06)	0.96
P_{O_2} (kPa)	2.22 (0.75)	1.98 (0.82)	0.35

Exclusion criteria were pre-existing or pregnancy-induced hypertension, known foetal abnormality or allergy to bupivacaine or meperidine. During the preoperative visit, written informed consent was obtained and additional instruction was given on the use of i.v. patient-controlled analgesia (PCA). Patients fasted overnight and were prescribed premedication of ranitidine 150 mg orally the evening before and on the morning of operation. On arrival at the operating theatre, 0.3 M sodium citrate 30 ml was given orally and 5 min later baseline systolic arterial pressure was calculated as the mean of three measurements taken at 2 min intervals, using the oscillometric method. A 16 G peripheral i.v. cannula was then inserted and 20 ml kg^{-1} lactated Ringer's solution given as preload. A 20 G peripheral i.v. cannula was also inserted for dedicated access for PCA.

Solutions for spinal anaesthesia were prepared under sterile conditions by the anaesthetist. Two millilitres of hyperbaric 0.5% bupivacaine was drawn into a 5 ml syringe, to which was added either 0.2 ml saline (saline group) or 0.2 ml preservative-free meperidine 5% (meperidine group). The dose of 10 mg of meperidine was chosen because this dose has previously been used intrathecally for labour analgesia.[12 13] Patients were allocated randomly to groups by selection of the uppermost envelope from a set of preshuffled envelopes containing a code. To facilitate blinding, the anaesthetist prepared two identical 1 ml syringes containing either saline or meperidine. The anaesthetist was kept blinded while the code was revealed to the scrub nurse, who selected the appropriate syringe and discarded the other. The contents of the selected syringe were then added to the bupivacaine.

After skin disinfection and infiltration with 1% lidocaine, lumbar puncture was performed with a 25 G pencil-point spinal needle at the L2–3 or L3–4 vertebral interspace with the patient in the lateral position. After free flow of cerebrospinal fluid had been confirmed, the study solution was injected intrathecally over approximately 20 s. Patients were then immediately placed supine with lateral tilt. Oxygen 4 litre min^{-1} was administered *via* a Hudson mask.

Standard monitoring was applied, including continuous pulse oximetry and ECG. Non-invasive arterial pressure was recorded each minute from the time of intrathecal injection until delivery, and then at 3 min intervals until the end of the operation. Hypotension, defined as a decrease in systolic arterial pressure to less than 90 mm Hg or a decrease of 25% from baseline, was treated with boluses of i.v. ephedrine 10 mg as required. Respiratory rate was measured as the number of carbon dioxide peaks that occurred during continuous carbon dioxide sampling via a catheter placed within the Hudson mask.

Times of skin incision, uterine incision and delivery were noted. After delivery, oxytocin 10 IU was given i.v. Apgar scores were recorded at 1 and 5 min. Samples of arterial and venous blood were taken from a double-clamped segment of umbilical cord for immediate blood gas analysis using a Ciba-Corning 850 blood gas analyser (Ciba-Corning, Medfield, MA, USA). Intraoperative pain and pruritus were assessed according to a three-point scale (0=symptom not present, 1=symptom present but not requiring treatment, 2=symptom present and treatment given on patient request). Intraoperative pain was treated with i.v. alfentanil 200 μg as required. Pruritus was treated with i.v. chlorphenamine 10 mg as required. Any instances of respiratory depression (defined as a respiratory rate of less than 12 breaths min^{-1}), shivering, or nausea or vomiting were recorded. Nausea or vomiting was treated with i.v. metoclopramide 10 mg after first excluding hypotension.

In the recovery room, PCA was made available using a Graseby 3300 PCA device (Graseby Medical, Watford, UK) that was programmed to deliver morphine as a bolus of 1 mg, with a lockout time of 8 min and no limit over time. We defined the duration of effective analgesia given by the study solution as the time from injection to the first PCA demand. Pulse rate and non-invasive arterial pressure measurements were recorded at 5 min intervals and arterial oxygen saturation was monitored continuously. The sensory level to pinprick was assessed every 30 min until regression of block to the level of T10 or below, after which patients were discharged to the ward. Duration of sensory block was defined as the time from intrathecal injection to regression of block to T10.

Postoperative ward monitoring of patients included assessment of sedation, respiratory rate, pulse oximetry and non-invasive arterial pressure every hour for 6 h and then at 2 h intervals. An anaesthetist was available at all times during the period of PCA use, with routine review of patients in the afternoon and evening of the day of operation and on the day after the operation. The time of first PCA demand and cumulative morphine consumption 2, 6 and 24 h after intrathecal injection were obtained from the electronic memory of the PCA device. Other information collected 24 h after operation included the occurrence of any side-

Table 2 Level of sensory block

Dermatome	Saline group (n=20)	Meperidine group (n=20)
C4	0	1
C5	1	1
C6	0	2
C7	0	0
C8	0	0
T1	0	0
T2	1	3
T3	7	4
T4	7	5
T5	3	4
T6	1	0

effects in the first 24 h and any incidence of residual neurological signs.

Sample size was determined prospectively using data from previous elective Caesarean sections performed under spinal anaesthesia in our institution. Power analysis indicated that 17 patients per group were required to detect a difference of 1 h in the time to first PCA demand (α=0.05, β=0.2). Assuming a potential dropout rate of 15%, we decided to recruit 20 patients per group. Statistical calculations were performed using SPSS 9.0 (SPSS, Chicago, IL, USA). We used Student's *t*-test to analyse continuous data and the Mann–Whitney *U*-test for non-continuous data. Dichotomous data were analysed with the χ^2 test. Duration of effective analgesia was described using the Kaplan–Meier survival curve and analysed with the log-rank test. A value of P<0.05 was considered statistically significant.

Results

We obtained consent from 40 patients, 20 of whom were randomized to each group. Morphine consumption data were not included in the statistical analysis for one patient in the saline group because a leak in the PCA delivery system prevented accurate measurement of drug consumption. Time to first PCA demand and morphine consumption data were excluded for two patients in the meperidine group because of accidental PCA demands before the onset of pain. In the saline group, a calibration error occurred with one umbilical vein sample and sufficient umbilical arterial blood could not be obtained for one patient. In the meperidine group, neither umbilical arterial nor venous blood could be sampled for one patient for technical reasons.

Maternal characteristics, except parity, were comparable in the two groups (Table 1). The meperidine group had greater parity (P=0.014). All patients had adequate sensory block for surgery. Block height for the saline group ranged from C5 to T6 and from C4 to T5 for the meperidine group (Table 2). The median level of block was T1–T2 for both groups. The times from spinal injection to incision, spinal injection to delivery and uterine incision to delivery and the duration of surgery were similar between groups. Neonatal outcome was also similar between groups.

Table 3 Incidence of adverse intraoperative events

	Saline group (n=20)	Meperidine group (n=20)	P
Hypotension	11 (55%)	14 (70%)	0.33
Intraoperative discomfort			
None	18 (90%)	20 (100%)	
Mild	1 (5%)	0 (0%)	
Severe	1 (5%)	0 (0%)	0.37
Shivering	8 (40%)	3 (15%)	0.16
Nausea/vomiting	3 (15%)	11 (55%)	0.02

Eleven patients in the meperidine group had nausea and vomiting after correction of hypotension compared with three patients in the saline group (P=0.02; Table 3). Ephedrine requirement was similar between groups. No patient had pruritus or respiratory depression. Two patients in the saline group complained of discomfort during surgery, one of whom received alfentanil 200 μg i.v.. There were no complaints of intraoperative discomfort from patients in the meperidine group.

Mean duration of sensory block was greater in the meperidine group (129 (SD 24.0) min) compared with the saline group (113 (21.5) min; P=0.028). The mean duration of effective analgesia was greater in the meperidine group (234 (95% confidence interval 200–269) min) compared with the saline group (125 (111–138) min, P<0.001) (Fig. 1). Two hours after intrathecal injection, mean cumulative morphine consumption was greater in the saline group (0.8 (1.3) min) compared with the meperidine group (0.1 (0.2) min; P=0.013) (Table 4). At 6 h, mean cumulative morphine consumption was greater in the saline group (12.8 (6.0) min) compared with the meperidine group (6.6 (5.2) min; P=0.002). At 24 h, mean cumulative morphine consumption was similar between groups. During the epoch between 6 and 24 h, mean morphine consumption was greater in the meperidine group (32.1 (9.6) mg) compared with the saline group (22.5 (11.0) mg; P=0.008).

Postoperative side-effects of nausea, pruritus and drowsiness were mild and similar between groups. No patient in either group showed respiratory depression whilst using PCA or had signs of residual neurological effects 24 h later.

Discussion

We found that the addition of meperidine to intrathecal hyperbaric bupivacaine increased the duration of effective analgesia after elective Caesarean section compared with placebo. Although postoperative pain relief after Caesarean section with intrathecal meperidine and bupivacaine mixtures has been described previously, there was no comparison with a placebo group.[14] Studies of the addition of other opioids to intrathecal bupivacaine in which postoperative PCA was used showed that fentanyl 15 μg increased the mean duration of effective analgesia from 124 to 184 min[15]

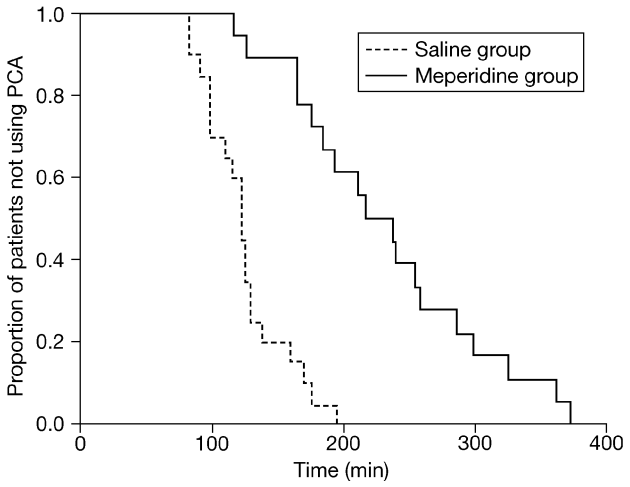

Fig 1 Survival curves showing duration of effective analgesia (time from intrathecal injection to first PCA demand). The broken line depicts the saline group (mean duration of analgesia 125 min (95% confidence interval 111–138)) and the solid line depicts the meperidine group (234.1 (200–269) min; $P<0.001$).

and diamorphine 0.25 mg increased the duration of effective analgesia up to a mean of 201 min compared with 75 min for placebo.[16] To our knowledge, data assessing postoperative analgesia using PCA have not been reported for intrathecal sufentanil and bupivacaine mixtures.

The assessment of morphine consumption by PCA provides an objective measurement of postoperative pain and analgesic requirements.[6 7 15–18] It has the advantages of accurate, objective assessment of the timing and titration of analgesic use by patients with a minimum of external interference. Additionally, data from different studies can be compared using the same end-points. We did not assess visual analogue scale pain scores in this study. Although inclusion of pain scores may have added further information on the patients' postoperative analgesic requirement, care must be taken in the interpretation of such data as pain scores are likely to be reduced by concurrent consumption of analgesics via PCA, resulting in convergence of data.

Although we found that the meperidine group had prolonged analgesia and less morphine consumption than the saline group up to 6 h after injection, conversely, during the period from 6 to 24 h, morphine consumption was greater in the meperidine group compared with the saline group, thus causing the overall cumulative morphine consumption at 24 h to be similar. The explanation of this finding is unclear. It is possible that the high local concentration of opioid introduced intrathecally may have induced either acute spinal opioid tolerance[19] or hyperalgesia.

Nausea and vomiting are troublesome side-effects encountered during spinal anaesthesia for Caesarean section. Possible aetiologies include hypotension and peritoneal manipulations that stimulate vagal afferents. With intrathecal opioids, a direct opioid effect can also be a factor. We found an increased incidence of intraoperative nausea or vomiting in the meperidine group compared with the saline group after correction of hypotension. Previously, intrathecal meperidine 10 mg alone was found to be associated with more nausea or vomiting than fentanyl and sufentanil when used in continuous spinal analgesia for labour analgesia.[20] Larger doses of intrathecal meperidine used as the sole agent for spinal anaesthesia in Caesarean section have also been associated with nausea or vomiting.[9–11] These studies indicate that intrathecal meperidine, in doses as low as 10 mg, can increase nausea or vomiting. In contrast, a review of randomized controlled trials of intrathecal opioids in spinal anaesthesia for Caesarean section concluded that nausea or vomiting does not increase with fentanyl or sufentanil, although it does with morphine.[4] Recently, intrathecal fentanyl has been shown to be more effective than i.v. ondansetron in preventing intraoperative nausea or vomiting during spinal anaesthesia for Caesarean section.[21] These data suggest that fentanyl may be a better choice than meperidine as an adjunctive intrathecal agent during spinal anaesthesia for Caesarean section when nausea and vomiting are considered.

Lipid-soluble opioids have been shown to decrease discomfort from intraoperative peritoneal manipulations when combined with intrathecal bupivacaine,[1 5 15 16] though the value of this has been questioned.[4] In our study, the incidence of intraoperative discomfort or pain during surgery was very small in both groups and there was thus insufficient statistical power to reveal a difference. Comparisons between studies should be made with care because differences in surgical technique may affect the amount of additional intraoperative analgesia required.

Pruritus has been associated with intrathecal fentanyl,[1 2] sufentanil,[3 22–24] diamorphine[16] and morphine.[5–7 25 26] In our study, no patient complained of pruritus during the operation and only a small number had pruritus afterwards. In studies in which the dose of intrathecal meperidine was 50 mg or greater, the incidence of pruritus ranged from 10.7 to 32%.[9–11] A dose-dependence study of intrathecal meperidine would demonstrate whether pruritus occurs in a dose-dependent fashion but would probably incur an undesirably high incidence of nausea and vomiting.

We found that regression of spinal anaesthesia was prolonged with patients who received intrathecal meperidine. This feature is consistent with other studies of

Table 4 Cumulative morphine consumption by patient-controlled analgesia (mean (SD))

Time after intrathecal injection (h)	Saline group (n=19)	Meperidine group (n=18)	P
2	0.8 (1.3)	0.1 (0.2)	0.013
6	12.8 (6.0)	6.6 (5.2)	0.002
24	35.3 (11.2)	38.7 (10.6)	0.35

co-administration of bupivacaine with lipid soluble opioids.[1–3 15] Intrathecal opioids potentiate the action of intrathecal local anaesthetics and the inherent local anaesthetic properties of meperidine may have contributed in our study.

Our patients had no neurological symptoms 24 h after operation. There are no reports in the literature to suggest that intrathecal meperidine is associated with long-term neurological dysfunction.[8] Respiratory depression has been reported with intrathecal meperidine but typically at doses above 50 mg or with concurrent use of other sedatives.[8 27] Unlike morphine, meperidine has not been reported to be associated with delayed respiratory depression. No patient in our study had respiratory depression either during or after the operation.

In summary, the addition of intrathecal meperidine 10 mg to hyperbaric bupivacaine prolonged analgesia after elective Caesarean section compared with placebo, although the duration of effective analgesia was limited to approximately 4 h. Meperidine has the advantages of being widely available and inexpensive. However, an important limitation of its use is increased intraoperative nausea and vomiting. Further studies, with prophylactic antiemetics or using smaller doses of meperidine, are required to determine whether nausea and vomiting can be reduced whilst maintaining an increased duration of postoperative analgesia.

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References

1 Hunt CO, Naulty JS, Bader AM, *et al*. Perioperative analgesia with subarachnoid fentanyl–bupivacaine for cesarean delivery. *Anesthesiology* 1989; **71**: 535–40

2 Belzarena SD. Clinical effects of intrathecally administered fentanyl in patients undergoing cesarean section. *Anesth Analg* 1992; **74**: 653–7

3 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

4 Dahl JB, Jeppesen IS, Jørgensen H, Wetterslev J, Møiniche S. Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia. *Anesthesiology* 1999; **91**: 1919–27

5 Abouleish E, Rawal N, Fallon K, Hernandez D. Combined intrathecal morphine and bupivacaine for cesarean section. *Anesth Analg* 1988; **67**: 370–4

6 Swart M, Sewell J, Thomas D. Intrathecal morphine for caesarean section: an assessment of pain relief, satisfaction and side-effects. *Anaesthesia* 1997; **52**: 373–7

7 Palmer CM, Emerson S, Volgoropolous D, Alves D. Dose–response relationship of intrathecal morphine for postcesarean analgesia. *Anesthesiology* 1999; **90**: 437–44

8 Ngan Kee WD. Intrathecal pethidine: pharmacology and clinical applications. *Anaesth Intensive Care* 1998; **26**: 137–46

9 Cheun JK, Kim AR. Intrathecal meperidine as the sole agent for Cesarean section. *J Korean Med Sci* 1989; **4**: 135–8

10 Kafle SK. Intrathecal meperidine for elective Caesarean section: a comparison with lidocaine. *Can J Anaesth* 1993; **40**: 718–21

11 Nguyen Thi TV, Orliaguet G, Ngû TH, Bonnet F. Spinal anesthesia with meperidine as the sole agent for cesarean delivery. *Reg Anesth* 1994; **19**: 386–9

12 Norris MC, Boreen S, Leighton BL, Mingey D, Kent H. Intrathecal meperidine for labor analgesia. *Anesthesiology* 1990; **73**: A983

13 Swayze CR, Skerman JH, Walker EB, Sholte FG. Efficacy of subarachnoid meperidine for labor analgesia. *Reg Anesth* 1991; **16**: 309–13

14 Chung JH, Sinatra RS, Sevarino FB, Fermo L. Subarachnoid meperidine–morphine combination. An effective perioperative analgesic adjunct for cesarean delivery. *Reg Anesth* 1997; **22**: 119–24

15 Shende D, Cooper GM, Bowden MI. The influence of intrathecal fentanyl on the characteristics of subarachnoid block for Caesarean section. *Anaesthesia* 1998; **53**: 706–10

16 Kelly MC, Carabine UA, Mirakhur RK. Intrathecal diamorphine for analgesia after Caesarean section. A dose finding study and assessment of side-effects. *Anaesthesia* 1998; **53**: 231–7

17 Graham D, Russell IF. A double-blind assessment of the analgesic sparing effect of intrathecal diamorphine (0.3 mg) with spinal anaesthesia for elective caesarean section. *Int J Obstet Anesth* 1997; **6**: 224–30

18 Husaini SW, Russell IF. Intrathecal diamorphine compared with morphine for postoperative analgesia after caesarean section under spinal anaesthesia. *Br J Anaesth* 1998; **81**: 135–9

19 Cooper DW, Lindsay SL, Ryall DM, Kokri MS, Eldabe SS, Lear GA. Does intrathecal fentanyl produce acute cross-tolerance to i.v. morphine? *Br J Anaesth* 1997; **78**: 311–3

20 Honet JE, Arkoosh VA, Norris MC, Huffnagle HJ, Silverman NS, Leighton BL. Comparison among intrathecal fentanyl, meperidine, and sufentanil for labor analgesia. *Anesth Analg* 1992; **75**: 734–9

21 Manullang TR, Viscomi CM, Pace NL. Intrathecal fentanyl is superior to intravenous ondansetron for the prevention of perioperative nausea during cesarean delivery with spinal anesthesia. *Anesth Analg* 2000; **90**: 1162–6

22 Courtney MA, Bader AM, Hartwell B, Hauch M, Grennan MJ, Datta S. Perioperative analgesia with subarachnoid sufentanil administration. *Reg Anesth* 1992; **17**: 274–8

23 Ngiam SK, Chong JL. The addition of intrathecal sufentanil and fentanyl to bupivacaine for caesarean section. *Singapore Med J* 1998; **39**: 290–4

24 Lin BC, Lin PC, Lai YY, Huang SJ, Yeh FC. The maternal and fetal effects of the addition of sufentanil to 0.5% spinal bupivacaine for cesarean delivery. *Acta Anaesthesiol Sin* 1998; **36**: 143–8

25 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

26 Cardoso MM, Carvalho JC, Amaro AR, Prado AA, Cappelli EL. Small doses of intrathecal morphine combined with systemic diclofenac for postoperative pain control after cesarean delivery. *Anesth Analg* 1998; **86**: 538–41

27 Ong B, Segstro R. Respiratory depression associated with meperidine spinal anaesthesia. *Can J Anaesth* 1994; **41**: 72