Effects of intrathecal and i.v. small-dose sufentanil on the median effective dose of intrathecal bupivacaine for Caesarean section

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Background. Spinal anaesthesia with bupivacaine combined with sufentanil has been widely used for Caesarean section. However, the main site of action (spinal vs central) of intrathecal (IT) sufentanil is controversial. The aim of this study was to examine the predominant mechanism of action of IT, small-dose sufentanil when added to bupivacaine for Caesarean section, by comparing the effects of IT and i.v. sufentanil 2.5 μg on the median effective dose (ED50) of bupivacaine.

Methods. Ninety parturients undergoing elective Caesarean section with a combined spinal–epidural technique were enrolled into this prospective, double-blind, up-down sequential allocation study. According to the up-down sequential allocation, parturients received varying doses of bupivacaine alone (C group) or co-administered with i.v. sufentanil 2.5 μg group (IVS group; n=30) or IT sufentanil 2.5 μg group (ITS group; n=30). The possible maternal or neonatal adverse effects were also recorded.

Results. The ED50 of bupivacaine was 6.3 mg (95% CI 6.2–6.5) in the C group, 5.2 mg (95% CI 5.1–5.4) in the IVS group, and 3.0 mg (95% CI 2.9–3.1) in the ITS group. The ED50 in the ITS group was significantly lower as compared with the other two groups (P<0.0005). With the exception of pruritus that exclusively occurred in the ITS group (P=0.011, compared with the other two groups), no significant differences among groups were observed regarding the frequencies of the maternal or neonatal adverse effects.

Conclusions. Compared with an equal dose of sufentanil i.v., intrathecally administered sufentanil 2.5 μg has a significant local anaesthetic-sparing effect via a predominantly spinal mechanism for Caesarean section.

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Spinal anaesthesia is a widely used technique for Caesarean section. Its quality can be improved by intrathecal (IT) addition of opioids to local anaesthetics. Sufentanil, the most lipophilic, clinically available opioid, is a common adjunct to local anaesthetics. However, there is a controversy regarding the predominant site of action (i.e. spinal or central) of IT sufentanil. Some clinical studies have suggested that IT administration of sufentanil may produce selective spinal analgesia. However, a supraspinal action of spinal sufentanil by either systemic absorption or cephalad spread within the cerebrospinal fluid (CSF) has also been implied. Therefore, further studies are needed to determine the predominant mechanism of action of spinal sufentanil and whether the IT administration route is rational.

Our aim in the present study was to examine the predominant mechanism of action of IT administered small-dose sufentanil. For this purpose, we used the up-down sequential allocation model to compare the IT and i.v. administered sufentanil 2.5 μg for their effects on the median effective dose (ED50) of bupivacaine for Caesarean section.
Methods

After Institutional Ethics Committee approval, 90 ASA I or II nulliparous parturients, after at least 37 weeks of gestation, undergoing elective Caesarean section were enrolled in this study after giving written informed consent. Exclusion criteria were pregnancy-induced hypertension, foetal heart rate abnormalities, body weight >100 kg or contraindications to regional anaesthesia. In a double-blinded, randomized, prospective study design, parturients were allocated into three groups: control group (C group), i.v. sufentanil 2.5 µg group (IVS group), and IT sufentanil 2.5 µg group (ITS group) (n=30). Randomization was achieved by means of the opaque sealed envelope technique that had been sorted by computer-generated random allocation.

Upon arrival at the operating theatre, oxygen 2 litre min⁻¹ was delivered routinely via nasal cannula. All parturients had an i.v. catheter inserted in a peripheral arm vein and were premedicated with i.v. metoclopramide 10 mg and ranitidine 50 mg for 30 min before anaesthesia. After an i.v. preload with 500 ml of lactated Ringer’s solution, combined spinal-epidural (CSE) technique was performed at the L3–L4 interspace with the parturient in the left lateral decubitus position. The epidural space was identified with a 16 gauge Tuohy needle using the loss of resistance to air technique. After lumbar puncture with a 26 gauge pencil-point needle passed through the Tuohy needle and the aspiration of CSF, the study solution was injected into the subarachnoid space >15 s with the orifice of the spinal needle in the cephalad direction. The spinal needle was withdrawn, and an epidural catheter was threaded 3 cm into the epidural space and secured. Parturients were immediately positioned supine with left uterine displacement. The parturients were randomly allocated into three groups of 30 each to receive either the designated dose of bupivacaine (0.5%) alone (both the C group and IVS group) or bupivacaine (0.5%) with sufentanil 2.5 µg (ITS group). The IT solutions were diluted with dextrose 10% to make a total volume of 3 ml, by one investigator who was not otherwise involved in the study. In the IVS group, sufentanil 2.5 µg (diluted with saline 0.9% to 2 ml) was immediately i.v. administered after IT injection, and the other two groups received a placebo i.v. administration of saline. The dose of bupivacaine received by a particular patient in each group was determined by the outcome in the previous parturient, according to the up-down sequential allocation technique. The dosing adjustment was 1 mg. However, the first patient was assigned to a dose of 9 mg based on our clinical experience. Neither the anaesthesiologist performing the anaesthetic procedure and subsequent assessment and management nor the parturient was aware of the dose administered and group allocation.

Sensory block was bilaterally tested in each dermatomal level for loss to pinprick sensation at regular 5 min intervals for 20 min. The first outcome was success, where the upper dermatomal level of loss of discrimination to pinprick was at or above T6 within 20 min of the IT injection. The parturient did not experience intraoperative pain or, although they experienced a little discomfort, epidural supplemental anaesthesia was not required during surgery. This outcome would direct a 1 mg dose decrement in the next patient assigned to that group. The second outcome was failure, where the upper dermatome level was below T6 within 20 min of the IT injection or despite attaining a T6 sensory level, supplemental anaesthesia was required at the request of the patient to complete surgery because of some visceral pain or discomfort. This outcome would direct a 1 mg dose increment in the next patient. In cases of failure, 5 ml of ‘rescue’ epidural lidocaine 2% was given and repeated as required.

Electrocardiogram, heart rate, and oxygen saturation were monitored continuously throughout the study. Non-invasive arterial pressure was measured at baseline (averaged over three measurements immediately before anaesthesia), at 1 min intervals from the time of IT injection until delivery, and thereafter at 5 min intervals until the end of surgery. The presence or absence of maternal adverse effects, including nausea, vomiting, pruritus, hypoxaemia, hypotension, and bradycardia, were also recorded. Hypotension was defined as a systolic blood pressure value of <90 mm Hg or a 20% decrease in systolic blood pressure compared with the baseline values; it was treated, if necessary, with i.v. boluses of ephedrine 5 mg. Bradycardia was defined as a heart rate value of <50 beats min⁻¹, which was treated with i.v. atropine 0.5 mg. Hypoxaemia was defined as oxygen saturation under 95%, which was treated with ventilatory support via facemask with higher oxygen flow. At delivery, blood samples were collected from the umbilical artery for blood gas and haemoglobin analyses. Apgar scores were determined at 1 and 5 min after delivery.

Statistical analysis

Data were presented as mean (SD), median (range), and count as appropriate. Analyses included one-way ANOVA, Kruskal–Wallis one-way analysis, and Fisher’s exact test as appropriate. The ED₅₀ with 95% CI of bupivacaine was estimated by the up-down reversals and by probit regression as a back-up or sensitivity analysis. Analyses were performed using the following software: the SPSS 10.0 for Windows statistical package (Chicago, IL, USA) and Excel 2000 (Microsoft Inc., Redmond, VA, USA). Based on a previous study¹² and an assumed SD of 1.8 mg, we estimated that a minimum of 26 patients in each group were required to detect a difference of 2 mg significant at P<0.05 (two-sided) with 0.8 power for an up–down sequential allocation design.
Results

All 90 patients enrolled completed the study according to the study protocol and were included in the analysis. Patients’ characteristics and the duration of surgical procedure were similar in the three groups (Table 1).

The sequences of success and failure doses of bupivacaine for the three groups are shown in Figure 1. The ED50 of bupivacaine was 6.3 mg (95% CI 6.2–6.5) in the C group, 5.2 mg (95% CI 5.1–5.4) in the IVS group, and 3.0 mg (95% CI 2.9–3.1) in the ITS group determined with the formula described by Dixon and Massey.11 The results of probit regression are presented in Table 2. The ED50 values in the ITS group were significantly lower compared with the other two groups (P<0.0005). However, the difference between the C group and the IVS group was not significant (P=0.103).

The frequencies of maternal adverse effects are summarized in Table 3. Seven patients in the ITS group reported pruritus intraoperatively compared with none in the other two groups (P=0.011). No significant differences among groups were observed regarding the frequencies of nausea, vomiting, bradycardia, hypotension, and the consumption of ephedrine. No patient in the three groups experienced desaturation.

The newborns showed no statistically significant differences among groups in weight, Apgar scores, umbilical cord arterial blood gas, and haemoglobin (Table 4). None of the newborns had an Apgar score <7.

Discussion

This is the first study to assess specifically the effects of IT and i.v. small-dose sufentanil on the ED50 for bupivacaine during Caesarean section under spinal anaesthesia. We have demonstrated that IT, but not i.v., administration of sufentanil 2.5 µg did have a dose-sparing effect on bupivacaine requirement for Caesarean section.

Spinal anaesthesia with bupivacaine alone or combined with opioids is a commonly used local anaesthetic technique for Caesarean section.1–4 As compared with other opioids such as fentanyl, sufentanil is a more potent adjunct to local anaesthetics with respect to the duration of effective analgesia.1,2 However, the site of action (spinal vs central) of intrathecally administered sufentanil has been controversial. Opioids are administered spinaly mainly with the aim of achieving selective spinal analgesia. Whether this goal is achieved depends on the rate and extent to which opioids distribute from the CSF to opioid receptors in the spinal cord dorsal horn. Because of the

Table 1 Patients’ characteristics and duration of surgery [data are mean (range or SD); P, not significant]

<table>
<thead>
<tr>
<th>Variable</th>
<th>C group (n=30)</th>
<th>IVS group (n=30)</th>
<th>ITS group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>29 (22–34)</td>
<td>26 (22–32)</td>
<td>28 (21–38)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69 (7)</td>
<td>67 (7)</td>
<td>65 (7)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161 (5)</td>
<td>159 (4)</td>
<td>158 (3)</td>
</tr>
<tr>
<td>Surgery time (min)</td>
<td>38 (8)</td>
<td>40 (10)</td>
<td>33 (6)</td>
</tr>
</tbody>
</table>

Table 2 ED50 for IT bupivacaine (mg) [data are ED50 (95% CI); *P<0.0005 compared with C and IVS groups using one-way ANOVA]

<table>
<thead>
<tr>
<th></th>
<th>C group (n=30)</th>
<th>IVS group (n=30)</th>
<th>ITS group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up-down analysis</td>
<td>6.3 (6.2, 6.5)</td>
<td>5.2 (5.1, 5.4)</td>
<td>3.0 (2.9, 3.1)*</td>
</tr>
<tr>
<td>Probit regression</td>
<td>6.0 (5.5, 6.5)</td>
<td>5.3 (4.8, 5.7)</td>
<td>2.9 (2.3, 3.4)*</td>
</tr>
</tbody>
</table>
extreme lipid solubility of sufentanil, it has a very large volume of distribution in the spinal cord with rapid clearance into the spinal cord vasculature and epidural space in a pig model, which implies that very little spinal sufentanil is available for interaction with spinal cord opioid receptors and suggests that systemic uptake may be as important as the effect at the dorsal horn. In another animal study, Adam and colleagues have demonstrated that the ratio for the ED50 of i.v. to IT sufentanil of 2.5 μg significantly decreased compared with bupivacaine alone or an equal i.v. administered dose of sufentanil. This means that addition of IT sufentanil 2.5 μg, but not i.v., markedly enhances the potency of spinal anaesthesia. Because other variables that could have influenced the spread of the spinal block (i.e. the patients' position or the site and speed of injection) were controlled and, in our opinion, the cephalad spread of spinal sufentanil within CSF would be largely limited in the case of a dose of 2.5 μg, this result is highly suggestive for a predominantly spinal mechanism of action for a small dose of IT sufentanil.

When epidurally administered, the mechanism of action of sufentanil appears to be related to the size of the dose. Although IT sufentanil 7.5 μg5 or 10 μg6 was reported to be superior to the i.v. route for analgesia, there has been no clinical study making such comparison with a smaller dose of sufentanil. Sufentanil in IT doses from 2.5 to 20 μg added to bupivacaine for Caesarean section have been reported. In this study, we chose a dose of 2.5 μg of sufentanil for several reasons: first, the incidence of adverse effects induced by IT sufentanil was dose dependent, and it is important to use the smallest effective opioid dose for Caesarean section to minimize potentially adverse maternal and neonatal risks; second, sufentanil in IT doses of 2.5 μg in conjunction with bupivacaine was similarly effective for Caesarean section compared with the doses of 5 μg1 or 7.5 μg; finally, we also thought that a smaller dose may be better to reflect the main mechanism of drugs in the spinal cord compared with a larger dose. This study demonstrated that the ED50 of bupivacaine with intrathecally co-administered sufentanil 2.5 μg significantly decreased compared with bupivacaine alone or an equal i.v. administered dose of sufentanil. This result, on the other hand, also supported the conclusion of a predominantly spinal mechanism of action for a small dose of IT sufentanil.

One plausible explanation for a possible contradiction between this study and animal studies may be the co-administration with bupivacaine. As Ginosar and colleagues have speculated, in the presence of local anaesthetics, the otherwise clinically insignificant spinal analgesic effect of IT sufentanil might become more pronounced and may even predominate. Alternatively, one drug may directly interact with the bioavailability of other drugs at the spinal cord.

The main adverse effects of intrathecally administered opioids include maternal respiratory depression, nausea, vomiting, and pruritus. With an IT dose of 2.5 μg of sufentanil, we could not find significant differences in the maternal adverse effects except for pruritus. Pruritus occurred exclusively in IT administration of sufentanil in this study. This result, on the other hand, also supported the conclusion of a predominantly spinal mechanism of action for IT sufentanil rather than a supraspinal effect by systemic redistribution to the brain. Hypotension, in this study, mostly occurred with systolic blood pressure values of 75–90 mm Hg while the lowest was 64 mm Hg (one patient with bupivacaine 8 mg in the C group).

In conclusion, intrathecally administered small-dose sufentanil produced a significant local anaesthetic-sparing effect primarily via a spinal site of action. Furthermore, except for pruritus, such a small dose of IT sufentanil did not increase maternal or neonatal adverse effects. Our result suggests that the IT combination of bupivacaine with a small dose of sufentanil is an appropriate choice for Caesarean section under spinal anaesthesia.
References