Patient-controlled epidural analgesia with sufentanil following Caesarean section: the effect of adrenaline and clonidine admixture

M. P. VERCAUTEREN, D. M. VANDEPUT, T. F. MEERT AND H. A. ADRIAENSEN

Summary
Sixty patients, scheduled for Caesarean section were randomly allocated to receive by the epidural route in a double-blind fashion one of the following patient-controlled analgesia mixtures for the relief of postoperative pain: sufentanil 2 μg.ml⁻¹ in 0.9% sodium chloride, sufentanil 2 μg.ml⁻¹ + adrenaline 2.5 μg.ml⁻¹, or sufentanil 2 μg.ml⁻¹ + clonidine 3 μg.ml⁻¹. Patient-controlled analgesia settings were a basal infusion rate of 2.5 ml.h⁻¹, an incremental dose of 2.5 ml. a lockout interval of 10 min and a 1-h limit of 10 ml. Whereas patient demographics and pain scores between the groups were not different, the 24-h consumption of sufentanil was significantly lower in the groups receiving a combination (167.5 SD 45 and 139.1 SD 31.9 μg for the adrenaline and clonidine groups respectively) as compared to the plain sufentanil regimen (208.2 SD 38.9 μg). Although sufentanil requirements were the lowest in the clonidine admixture group, there were no differences with regard to sedation as compared to the plain sufentanil group. The quality of sleep appeared to be significantly better in the sufentanil/adrenaline group despite a significantly lower degree of sedation and higher incidence of pruritus. Treatment of pruritus with naloxone did not seem to influence the quality of analgesia.

Key words
Pain; postoperative. Anaesthetic techniques, regional; epidural. Analgesics; sufentanil. Sympathetic nervous system; adrenaline, clonidine.

Method
The study was approved by the hospital ethics committee. After obtaining informed consent, 60 patients scheduled for elective or semi-urgent Caesarean section were considered for inclusion in the study. The evening before and 2 h before operation ranitidine 150 mg was given orally for prophylaxis against acid pulmonary aspiration. In all cases, the anaesthetic technique was a combined spinal-epidural (CSE) block. Prior to establishment of the block an intravenous fluid load of 1500 ml of compound sodium lactate solution was administered. After penetration of the dura, isobaric bupivacaine 8 mg and sufentanil 4 μg (i.e. 4 ml of a solution containing 4 ml of bupivacaine 0.25% and 1 ml or 5 μg of sufentanil) was slowly injected intrathecally. After removal of the spinal needle, a 20 G epidural catheter (Perifix®, Braun) was placed epidurally. The level of the block height, tested with ether, had to be at least T₃ before the surgeon was allowed to start. If after 15 min the upper
increments of local anaesthetic (lignocaine connected to a PCA pump (Bard given alone (group
level of sensory block appeared to be insufficient, further
administered via the epidural catheter.

Treatments were allocated in a randomised fashion and
complained of pain, an initial bolus of 2.5
solutions were prepared in a double-blind manner. The
recorded. Vital parameters were recorded by the midwives
tered after which the pumps were started.

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tated after which the pumps were started.

Retrospective visual analogue scale scores (rVAS) were
recorded at 10 and 24 h, and assessments made of quality
of night rest (poor, moderate, excellent), sedation (none,
moderate, marked), and pruritus. The overall consump-
tion and the number of bolus doses per 24 h were also
recorded. Vital parameters were recorded by the midwives
every 2 h during the first 6 h and thereafter at 4 h intervals.

When patients complained of inadequate pain relief, despite adequate use of the PCA pump, scored pain higher
than 3 on the VAS or required maximum doses for at least 2 consecutive hours, the PCA settings were increased to
4 ml (sufentanil 8 µg) for the infusion and bolus with a
maximum hourly dose of 15 ml (sufentanil 30 µg).
Additional pain relief was provided with intravenous para-
cetamol (Pro-Dafalgan®), if the maximum sufentanil dose
would have to be exceeded. When patients made no addi-
tional demands above the continuous infusion for at least 6
consecutive hours, the PCA settings were decreased to
2 ml h⁻¹ (4 µg h⁻¹) for the infusion and 2 ml (4 µg) per
demand dose, but maintaining the previous maximum
hourly limit. If patients complained of intolerable pruritus,
naloxone 0.2 mg was administered intravenously. Urinary
retention was not evaluated since the majority of patients
had an indwelling bladder catheter.

The PCA pump remained connected to the patient for
the first 48 h, after which the epidural catheters were
removed. Only the data of the first 24 h were considered
for statistical analysis. Statistical analysis was performed using
the Mann–Whitney U-test and the Fisher’s Exact test as
appropriate. A value of p < 0.05 was considered to be
significant.

Results
Patient details are presented in Table 1. There were no
differences between the three groups with regard to age,
weight, parity, the gestation of pregnancy or the indication
for the surgical intervention. The interval between surgery
and the start of PCA, and retrospective resting pain scores
at 10 and 24 h were also comparable for all groups (Table 2).

Patients treated with plain sufentanil (SS group) used
208.2 (SD 38.9) µg sufentanil during the first 24 h.
Sufentanil requirements during the first 24 h were signifi-
cantly reduced in the groups receiving a combination with
adrenaline (167.5 SD 45 µg, p < 0.01) and clonidine (139.1

<table>
<thead>
<tr>
<th>Table 1. Patient details. Results are expressed as mean (SD).</th>
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</thead>
<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>Age; years</td>
</tr>
<tr>
<td>Weight; kg</td>
</tr>
<tr>
<td>Gestation; weeks</td>
</tr>
<tr>
<td>Parity; nulliparous/multiparous</td>
</tr>
<tr>
<td>Indication for procedure</td>
</tr>
<tr>
<td>Hypertension; pre-eclampsia</td>
</tr>
<tr>
<td>Fetal distress, intra-uterine growth retardation</td>
</tr>
<tr>
<td>Labour-related</td>
</tr>
<tr>
<td>Placenta praevia</td>
</tr>
</tbody>
</table>

There were no statistical differences between the three groups.
SS, plain sufentanil; SA, sufentanil + adrenaline; SC, sufentanil + clonidine.

<table>
<thead>
<tr>
<th>Table 2. Pain relief data. Results are expressed as mean (SD).</th>
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</thead>
<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>Interval birth-start PCA; min</td>
</tr>
<tr>
<td>Visual analogue score at 10 h</td>
</tr>
<tr>
<td>Visual analogue score at 24 h</td>
</tr>
<tr>
<td>Consumption of sufentanil. 24 h⁻¹; µg</td>
</tr>
<tr>
<td>Number of valid demands. 24 h⁻¹</td>
</tr>
<tr>
<td>Settings increased</td>
</tr>
<tr>
<td>Settings decreased</td>
</tr>
</tbody>
</table>

ns, not significant; *p < 0.05, **p < 0.01, ***p < 0.001 as compared to the SS group; §p < 0.05 as compared to
the SA group.
Table 3. Side effects. Results are expressed as numbers of patients.

<table>
<thead>
<tr>
<th>Group</th>
<th>SS</th>
<th>SA</th>
<th>SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itching</td>
<td>3</td>
<td>11*</td>
<td>5</td>
</tr>
<tr>
<td>Sedation:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>marked</td>
<td>5</td>
<td>1</td>
<td>6§</td>
</tr>
<tr>
<td>moderate</td>
<td>9</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>none</td>
<td>6</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Quality of sleep:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bad</td>
<td>7</td>
<td>1*</td>
<td>4</td>
</tr>
<tr>
<td>moderate</td>
<td>6</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>good</td>
<td>7</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

*p < 0.05 as compared to the SS group; §p < 0.05 as compared to the SA group.

SD 31.9 μg, p < 0.001), with the difference between the adrenaline group and the clonidine group also reaching statistical significance (p < 0.05).

The PCA settings were increased in three patients of the SS group as compared to only one patient in the groups receiving a combined regimen (not significant). In the clonidine group, they were decreased in eight patients as opposed to only one patient (p < 0.05) in the plain sufentanil group. The highest daily dose requirements were recorded for a patient in the plain sufentanil group (283 μg) whereas the lowest was in a patient receiving clonidine (104 μg).

Although the number of demands was significantly lower (p < 0.001) in both regimens containing a mixture, this was not apparent in improved quality of sleep (Table 3). Surprisingly, the group receiving adrenaline, in spite of more pruritus than the plain sufentanil group (p < 0.05) and less sedation than the clonidine-treated patients (p < 0.05), scored significantly better with regard to the quality of nights rest. Two patients in the SA group requested treatment for pruritus; naloxone 0.2 mg given intravenously made these patients comfortable. Analgesic requirements and pain scores did not change following this treatment. A transient decrease of the systolic blood pressure to 90 mmHg was recorded in two patients in the SC group; in one patient this might have been caused by marked blood loss. In both patients a moderate fluid load led to a rapid improvement.

Discussion

Adrenaline and clonidine both have alpha 2 adrenergic agonist properties and have been administered via the epidural route. The use of more specific alpha 2 adrenergic receptor agonists has been fuelled by the search for an effective alternative to central opioid therapy, with its side-effects such as respiratory depression, pruritus and urinary retention, for the management of pain.

In one of the first studies performed using clonidine to treat postoperative pain, Gordh gave post-thoracotomy patients either clonidine (3 μg.kg⁻¹) or saline [4]. There was no decrease in pethidine requirements in the clonidine-treated group. In an open study, patients after total knee arthroplasty or abdominal surgery received clonidine in doses ranging from 100 to 900 μg. Analgesia lasting more than 5 h was produced with the highest dose [5]. Transient sedation was a feature at the higher doses, probably because of high blood levels. There would appear to be conflicting evidence with regard to the clinical effectiveness of epidural clonidine for the treatment of acute pain. Whereas Gordh et al. found clonidine, up to 3 μg.kg⁻¹, to be completely ineffective for post-thoracotomy pain, lower doses, up to 2 μg.kg⁻¹, were shown to produce satisfactory pain relief for 3–4 h after orthopaedic and minor perineal surgery [6]. Equally conflicting are the reports of a synergistic effect of combining opioids with clonidine for postoperative pain relief. Mok et al. found no increased quality or duration of pain relief after combining nalbuphine with 75 μg clonidine as compared to nalbuphine alone [7]. Other investigators, on the other hand, have shown a synergistic effect when morphine was combined with clonidine [8, 9]. Sufentanil, in a dose of 50 μg, appeared to offer inferior pain relief as compared to a combination of 25 μg with clonidine 1 μg.kg⁻¹, but this was achieved at the expense of arterial hypotension with the combined regimen [3].

Although the alpha 2 adrenergic properties are less pronounced for adrenaline, Collins et al. using a decerebrate, spinal cord-transected cat model, demonstrated that adrenaline suppressed noxiously evoked activity in Wide Dynamic Range (WDR) neurones in the dorsal horn of the spinal cord [10]. Therefore, adrenaline may act directly on the spinal cord to enhance or prolong analgesia by modulating neurotransmission. In spite of these proven antinociceptive properties, adrenaline, unlike clonidine, has never been administered solely to relieve pain after surgery or in chronic pain conditions. With regard to vasoconstrictor agents, a decrease in the vascular uptake of the opioid remains an attractive hypothesis whereby more molecules of opioid may be available for storage in the epidural fat or for transdural penetration, thus increasing concentrations within the cerebrospinal fluid; the question arises whether this is also true for continuous administration. A review of the literature on the effects of adrenaline addition to lipophilic opioids administered epidurally demonstrates that the aforementioned hypothesis does not always relate to clinical experience (Table 4). As shown by some, but not all clinical reports, the addition of adrenaline to these substances may offer advantages in terms of prolonged duration of analgesia [11–21]. Systemic resorption may cause somnolence, nausea and vomiting within the first 30 min after injection of lipophilic opioids. Plasma concentrations of opioids were measured in five studies but significant reductions after adrenaline admixture could not be shown in two [16, 17]. Of the side effects, lower end-tidal carbon dioxide levels were the most striking finding [18]. The lack of agreement between all these studies may be related to the extremes in adrenaline doses, ranging between 25 and 75 μg.

Since lipophilic opioids do not tend to migrate rostrally in the cerebrospinal fluid, the addition of adrenaline should not increase the incidence of late onset respiratory depression as described with morphine [22].

The results of the present study confirm that the addition of adrenaline to sufentanil may be beneficial in terms of analgesic drug requirements and the degree of sedation. A reduced need for analgesic therapy in a less sedated mother may better allow her to care for her baby and breastfeed, without fear of causing neonatal sedation. The increased incidence of pruritus is the only observed disadvantage of this combination but confirms the findings of two other studies [11, 12]. The regimen including clonidine
was not significantly different as compared to patients versus a fentanyl-clonidine combination with others who compared continuous infusion of fentanyl appeared to be the best in terms of sufentanil requirements and was achieved without the hypotension reported after treated with plain sufentanil. Our results are in accordance may also be attributed to the frequent check-ups by the midwives, noises made by other patients sharing the same consumption. The addition of adrenaline has some advan-

ditional demands nor the presence of side effects. The hypo-


References


