Prevention of postoperative nausea and vomiting after spinal morphine for Caesarean section: comparison of cyclizine, dexamethasone and placebo

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Background. Low-dose intrathecal (spinal) morphine (0.1–0.2 mg) for Caesarean section delivers excellent postoperative analgesia but is associated with significant nausea and vomiting. We compared the antiemetic efficacy of cyclizine, dexamethasone, and placebo in this clinical setting.

Methods. Ninety-nine women undergoing elective Caesarean section under spinal anaesthesia were allocated randomly, in a double-blind study design, to receive either cyclizine 50 mg, dexamethasone 8 mg, or placebo as a single-dose infusion in saline 0.9%, 100 ml on completion of surgery. Spinal anaesthesia consisted of: hyperbaric bupivacaine 0.5%, 2.0 ml; fentanyl 10 μg; and spinal morphine 0.2 mg. The primary outcome measure was the incidence of nausea.

Results. The incidence of nausea was significantly less in patients receiving cyclizine compared with dexamethasone and placebo (33% vs 60 and 67%, respectively, P<0.05). Severity of nausea and number of vomiting episodes were also less at 3–6 h in cyclizine patients. Overall satisfaction with postoperative care at 24 h, expressed on a 100 mm visual analogue scale, was greater in cyclizine [78 (28)] than either dexamethasone [58 (31), P=0.03] or placebo [51 (28), P=0.008].

Conclusion. We conclude that following spinal morphine 0.2 mg and fentanyl 10 μg analgesia for Caesarean section, cyclizine 50 mg i.v. reduces the incidence of nausea compared with dexamethasone 8 mg i.v. or placebo. It also lessens the severity of nausea and vomiting, and increases maternal satisfaction in the early postoperative period.

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Low-dose intrathecal (spinal) morphine, first made popular more than a decade ago, has become established as an effective analgesic regimen after Caesarean section.¹–³ However, it is associated with a significant incidence of postoperative nausea and vomiting (PONV). The number of patients given 0.05–0.25 mg spinal morphine needed to harm one individual is 6.3 (95% CI 4.2–12.5) for nausea and 10.1 (95% CI 5.7–41.0) for vomiting.³

Among a number of antiemetic agents available for PONV after Caesarean section is dexamethasone, a corticosteroid with proven antiemetic efficacy after single-dose administration in chemotherapy and for PONV associated with general anaesthesia.⁴–⁸ It has also been demonstrably effective in reducing PONV in women receiving epidural morphine for pelvic surgery, including Caesarean section.⁹–¹¹ However, there are no reports investigating dexamethasone antiemetic therapy after spinal morphine for Caesarean section. Furthermore, cyclizine, a long-established, safe antiemetic with antihistamine and anticholinergic effects, has not been evaluated in this clinical setting either.

Therefore, we undertook a randomized, double-blind, placebo-controlled, clinical trial comparing standard, single-dose dexamethasone and cyclizine, in terms of their...
preventive efficacy for PONV and adverse effects, in women receiving spinal morphine for Caesarean section under regional anaesthesia.

Methods
The protocol was approved by Leicestershire Ethics Committee and informed written consent was obtained from all eligible patients. Ninety-nine women (ASA Grade I or II) presenting for elective Caesarean section under regional anaesthesia were invited to participate in this trial. Exclusion criteria were: patients for whom regional anaesthesia was declined or contraindicated; allergy to cyclizine, dexamethasone, prochlorperazine, opioids, or local anaesthetics; patients with pregnancy-induced hypertension or glucose intolerance; patients with established gastrointestinal diseases; and those who had taken antiemetic medication in the previous 24 h.

A histamine (H₂) antagonist (oral ranitidine 150 mg) was given the evening before and the morning of surgery. Surgical anaesthesia to T₄ dermatome level was provided by: hyperbaric bupivacaine 0.5%, 2.0 ml; fentanyl 0.2 ml (10 μg); and preservative-free morphine 0.2 ml (0.2 mg) for spinal injection, given via a 26G Whitacre pencil point needle, as part of a combined spinal epidural technique. The L₃–₄ or L₄–₅ intervertebral space was identified by loss of resistance to saline using a Tuohy 16G needle under aseptic conditions. Hartmanns’ solution 500 ml was infused before surgery and estimated fluid deficit and maintenance fluid requirements were infused as required during the case. If supplementary analgesia was required during surgery, lidocaine 2%, 3–5 ml was administered via the epidural catheter as required. Dermatomal sensory level was determined by ethyl chloride spray 10–15 min after the intrathecal injection. All patients received ephedrine 3–6 mg i.v. as required for hypotension at the discretion of the anaesthetist and also oxytocin 10 international units and i.v. antibiotics (augmentin 1.2 g, erythromycin 1 g if allergic to penicillins) after delivery. Finally, all patients received rectal diclofenac 100 mg at the end of surgery.

In the recovery room, patients were allocated randomly to receive a 100 ml infusion of trial medication over 10 min according to one of three group allocations. Blocked randomization in groups of nine was used, with each patient’s group allocation placed in a consecutively numbered scaled envelope. Patients allocated to cyclizine therapy received cyclizine 50 mg in saline 0.9%, 100 ml. Patients allocated to dexamethasone received dexamethasone 8 mg in saline 0.9%, 100 ml, while control patients received an infusion of saline 0.9%, 100 ml as placebo. These infusions were prepared by the anaesthetist in charge of the case, but out of sight of the patient. This anaesthetist took no further part in the data collection, and patients were therefore unaware to which group they had been allocated. The randomization process and identity of study drugs were also blinded from the research nursing staff that gathered the outcome data. Sedation was assessed by the researchers using the scale provided, severity of nausea and vomiting was defined by the patient using the scale provided, rescue antiemetic use was checked on the drug chart and patient satisfaction by asking the patient to use the scale provided. Patients experiencing a persistent nausea score of more than 1 or who had two or more vomiting episodes received prochlorperazine 12.5 mg i.m. rescue antiemetic medication on demand at 4 h intervals.

The primary outcome measure was the incidence of nausea in the first 24 h after surgery. Secondary outcome measures included the incidence of vomiting, incidence of requirement for rescue antiemetic medication, patient satisfaction with overall postoperative care at 24 h (measured on a 100 mm visual analogue scale (VAS), where 0 mm indicated total dissatisfaction and 100 mm indicated total satisfaction during the first 24 h of postnatal care). Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit; vomiting was defined as rhythmic contractions of the abdominal muscles with or without expulsion of gastric contents from the mouth (i.e. including retching). Secondary outcome measures were quantitatively documented as follows: severity of nausea (measured on a four point scale: 0=no nausea; 1=mild; 2=moderate; and 3=severe nausea); number of vomiting episodes; pain intensity, which was measured on a 100-mm VAS, 0 mm=no pain and 100 mm=intolerable pain. If rescue analgesia was required, patients received a single tablet containing codeine 300 mg and paracetamol 500 mg combined. Pruritus was measured on a four point categorical scale similar to that for nausea (0=no pruritus, 1=mild, 2=moderate, 3=severe pruritus). If treatment was needed, chlorpheniramine 4 mg orally was given. Sedation was also evaluated on a four-point scale (0=awake; 1=mild, eyes closed occasionally; 2=asleep, eyes closed unless spoken to; 3=severe sedation, requiring physical arousal to open eyes). Data were recorded by staff unaware of the group allocations at the end of the 3, 6, 12, and 24 h time slots after surgery. Patients were asked to report any adverse event (e.g. vomiting) that had occurred in the time periods 0–3, 3–6, 6–12, and 12–24 h, not just their present state at the particular time they were seen on the ward.

Sample size was determined prospectively. Because nausea is more prevalent than vomiting after spinal morphine, in the region of 60%,¹⁻³ we decided that a 35% reduction in the proportion of patients with any incidence of nausea would be clinically significant. The α-error (two-sided) was set at 0.05, the β-error at 0.1 (study power 90%). Therefore, we calculated that n=33 patients would be required in each group. Data were inspected for distribution using scattergrams and the Kolmogorov–Smirnov test. Statistical analysis was conducted using SPSS v9 for Windows. Non-normally distributed data (severity of nausea, number of vomiting episodes, pruritus, sedation patient characteristics, VAS pain scores, arterial pressure...
and ventilatory frequency) were compared by the Kruskal–Wallis test to identify differences between the three groups with post-hoc Mann–Whitney tests to detect differences between pairs of groups. Categorical variables (incidence of nausea, vomiting and requirement for rescue medication) were analysed by $\chi^2$ analysis of 3×2 contingency tables or Fisher’s exact test as appropriate, followed by similar analysis 2×2 tables for intergroup differences.

**Results**

Of the 99 parturients enrolled, nine patients did not complete the trial for the reasons outlined in Figure 1. In four cases, the study records were misplaced on the ward and were never traced. Two patients who were to undergo Caesarean section for breech presentation were withdrawn because ultrasound examination indicated cephalic presentation. Therefore, 90 patients (n=30 each group) completed the trial. The trial was initially powered at 90% requiring 99 patients: repeating the calculation for 80% power gives 22 patients per group so our study with 90 patients has a power between 80 and 90%. Baseline patient characteristics and duration of surgery are shown in Table 1. During the 24-h observation period, 20 patients in the cyclizine group compared with 18 in the dexamethasone group and 21 in the placebo group received supplementary oral analgesia (not significant). The time to rescue analgesia was not recorded.

The total incidence of any nausea, vomiting, and requirement for rescue medication is shown in Table 2. For each of these variables, cyclizine patients had significantly less nausea and vomiting than either dexamethasone or placebo, and dexamethasone was not significantly different from placebo. The median (range) number of rescue antiemetic injections given to each patient was 1 (0–3) in each group. The severity of nausea, rated on the four point categorical scale, was significantly reduced in cyclizine patients compared with both dexamethasone and placebo patients, at 3 and 6 h but not at 12 and 24 h (Table 3). The number of vomiting episodes was significantly decreased in cyclizine patients compared with placebo at 3 and 6 h and significantly less than dexamethasone patients at 3 h only (Table 3).

Overall satisfaction with postnatal care, rated on a VAS at 24 h, is shown in Table 4. Satisfaction was relatively low in both placebo and dexamethasone groups [mean 51 (SD 28) and 58 (31), respectively], with no significant difference between them. However, cyclizine was associated with significantly higher satisfaction than either of the other two groups. Highest and lowest pain scores in the observation period are also shown in Table 4. All parturients reported low pain scores and differences among the groups were not significant. In contrast, the incidence of pruritus was high in all groups (77–83%), but there were no significant differences between them. Systolic arterial pressures (SAP), ventilatory frequency, and sedation were all clinically unremarkable and also not significantly different between the groups.

![Fig 1 Study profile.](image-url)

### Table 1 Patient characteristics. Values are mean (SD or range) or median [range]

<table>
<thead>
<tr>
<th></th>
<th>Cyclizine (n=30)</th>
<th>Dexamethasone (n=30)</th>
<th>Placebo (n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>31.8 (20–38)</td>
<td>30.9 (22–37)</td>
<td>32.4 (21–36)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.8 (7.5)</td>
<td>70.1 (5.9)</td>
<td>69.6 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>50 (7)</td>
<td>53 (8)</td>
<td>48 (5)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2 Incidence of nausea, vomiting and requirement for rescue antiemetic therapy. Values refer to number (%) of patients

<table>
<thead>
<tr>
<th></th>
<th>Cyclizine (C) (n=30)</th>
<th>Dexamethasone (D) (n=30)</th>
<th>Placebo (P) (n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea at any time</td>
<td>10 (33)</td>
<td>18 (60)</td>
<td>20 (67)</td>
<td>P=0.02, C vs P</td>
</tr>
<tr>
<td>Vomiting at any time</td>
<td>9 (30)</td>
<td>17 (57)</td>
<td>18 (60)</td>
<td>P=0.04, C vs D</td>
</tr>
<tr>
<td>Rescue antiemetic given at any time</td>
<td>4 (13)</td>
<td>17 (57)</td>
<td>19 (63)</td>
<td>P=0.001, C vs D</td>
</tr>
</tbody>
</table>

**Table 4**

- Overall satisfaction with postnatal care
- Highest and lowest pain scores
- Systolic arterial pressures (SAP)
- Ventilatory frequency
- Sedation

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ising the quality of analgesia, by using lower intrathecal opioids in our unit, and this study has helped to demonstrate a reduction in PONV by any effective agent compared with both dexamethasone and placebo, but dexamethasone was no more effective than placebo. The number of vomiting episodes and severity of nausea were also significantly reduced by cyclizine, and overall satisfaction with their postoperative care was significantly higher in patients receiving cyclizine, compared with either dexamethasone or placebo. These findings conflict with the published efficacy of dexamethasone for prevention of PONV in patients receiving general anesthesia or epidural morphine.4–12

Although use of intrathecal morphine is associated with a high incidence of PONV, it provides excellent, safe analgesia for up to 24 h after surgery.1–3 We allowed an untreated placebo group because this was the first use of intrathecal opioids in our unit, and this study has helped to provide local baseline data for the incidence of nausea and vomiting in this clinical setting. There is emerging evidence that the incidence of PONV is reduced, without compromising the quality of analgesia, by using lower intrathecal doses of morphine, in the region of 0.1 mg.20

The mechanism of the antiemetic effects of dexamethasone is unclear. Glucocorticoid receptors are found in the nucleus of the solitary tract, the raphe nucleus, and the area postrema,13 all of which are involved in the regulation of nausea and vomiting.14 It is conceivable therefore that dexamethasone may affect PONV by modulating neurotransmission or receptor density in these nuclei.

Nonetheless, it is surprising that dexamethasone was ineffective after spinal morphine, when it has been consistently effective in reducing PONV after epidural morphine.9–12 Clearly, higher doses of morphine are used for epidural analgesia than spinal analgesia. Epidural opioids cause a higher incidence of PONV than spinal opioids after Caesarean section,15 therefore it may be easier to demonstrate a reduction in PONV by any effective agent when epidural morphine is used. However, our incidence of PONV after spinal morphine was 60–67% in the control group, which is at the upper end of the range quoted for epidural morphine.8–12 It is noteworthy that dexamethasone was ineffective after intrathecal neostigmine analgesia for inguinal herniotomy.16 Possibly, the mechanism of emesis induced by drugs administered via the intrathecal route differs from drugs given via the epidural route. Perhaps dexamethasone’s antiemetic effect is greater when brain stem nuclei are stimulated by opioids given via the epidural, rather than the intrathecal route, but this is speculative. Delayed postoperative gastric emptying has been shown in patients receiving spinal morphine and bupivacaine,17 but whether this contributes to emesis after epidural administration of these agents is unknown.

Cyclizine is a long-established, possibly underestimated, antiemetic with antihistaminic and anticholinergic properties, which may cause dry mouth and sedation.14-18 However, our data showed no evidence of increased sedation in patients receiving cyclizine compared with dexamethasone or placebo, although we did not specifically ask about cholinergic adverse effects. Cyclizine is both highly effective and well-tolerated and has been shown to be as effective as ondansetron for PONV after day-case laparoscopy.18 Others have recently confirmed that cyclizine, combined with ondansetron, decreased the incidence of vomiting after gynaecological laparoscopy from 20 to 3%, compared with ondansetron alone, with minimal reported side-effects.19

The incidence of PONV observed in the present study was high (60–67%). This may reflect our choice of dose of spinal morphine (0.2 mg), which is at the higher end of the

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### Table 3

<table>
<thead>
<tr>
<th>Cyclizine (C)</th>
<th>Dexamethasone (D)</th>
<th>Placebo (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea at 3 h</td>
<td>0 (0–1)*</td>
<td>1 (0–2.5)</td>
</tr>
<tr>
<td>Nausea at 6 h</td>
<td>0 (0–1)*</td>
<td>1 (0–1.5)</td>
</tr>
<tr>
<td>Nausea at 12 h</td>
<td>0 (0–0)</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td>Vomiting at 3 h</td>
<td>0 (0–1.5)*</td>
<td>1.5 (0–2.5)</td>
</tr>
<tr>
<td>Vomiting at 6 h</td>
<td>0 (0–1)*</td>
<td>1.5 (1–3)</td>
</tr>
<tr>
<td>Vomiting at 12 h</td>
<td>0 (0–0)</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td>Vomiting at 24 h</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
</tr>
</tbody>
</table>

### Table 4

<table>
<thead>
<tr>
<th>Cyclizine (C)</th>
<th>Dexamethasone (D)</th>
<th>Placebo (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall VAS satisfaction with Postoperative care (mm)</td>
<td>78 (50–100)</td>
<td>58 (25–85)*</td>
</tr>
<tr>
<td>Pain VAS highest</td>
<td>2.0 (0–5)</td>
<td>2.4 (1–5)</td>
</tr>
<tr>
<td>Pain VAS lowest</td>
<td>0.5 (0–3)</td>
<td>1.0 (0–3)</td>
</tr>
<tr>
<td>Incidence pruritus, n (%)</td>
<td>23 (77)</td>
<td>25 (83)</td>
</tr>
<tr>
<td>Pruritus highest score</td>
<td>1.5 (0–3)</td>
<td>1.5 (0–3)</td>
</tr>
<tr>
<td>Sedation highest score</td>
<td>0.6 (0–2)</td>
<td>0.2 (0–1)</td>
</tr>
<tr>
<td>SAP highest, mm Hg</td>
<td>112 (21)</td>
<td>114 (12)</td>
</tr>
<tr>
<td>SAP lowest, mm Hg</td>
<td>106 (11)</td>
<td>108 (18)</td>
</tr>
<tr>
<td>Ventilatory frequency/min lowest</td>
<td>18 (2)</td>
<td>17 (2)</td>
</tr>
</tbody>
</table>

*VAS=visual analogue scale for pain or patient satisfaction with postoperative care, as indicated. SAP=systolic arterial pressure.
range commonly used clinically. There is conflicting evidence on whether increasing the dose of spinal morphine above 0.1 mg increases the incidence of PONV. A recent meta-analysis suggested spinal morphine 0.1 mg as the optimum dose for balancing analgesic efficacy against dose-related increased incidence of PONV, but a dose-finding study in Caesarean section patients where up to 0.5 mg spinal morphine was administered found no increase in PONV compared with lower doses. Our study had been approved and was being conducted when this guideline emerged. In practice, many units continue to administer spinal morphine in doses of 0.15–0.2 mg. Our dose of dexamethasone (8 mg) is also consistent with the recommendation of a dose-finding study for its use after epidural morphine, which indicated that dexamethasone 5 and 10 mg were equally effective. We chose not to study 5-HT3 antagonists (e.g. ondansetron and granisetron), which, though effective in PONV, are expensive and can also contaminate breast milk. The fact that dexamethasone’s proven efficacy in PONV after general anaesthesia and epidural morphine was not reproduced in our study using spinal morphine, suggests that the efficacy of all antiemetics should be re-evaluated in this clinical scenario. However, our antiemetic drugs were administered in the recovery room and their efficacy assessed for the following 24 h. Dexamethasone is thought to have a late-onset antiemetic effect, which may have contributed to its disappointing lack of efficacy in this instance.

Our finding of significantly lower satisfaction with overall postoperative care in patients receiving placebo or dexamethasone medication, whose PONV was poorly controlled relative to cyclizine patients, is a true outcome measure of the success of PONV therapy and is indeed remarkable. It suggests that PONV is a significant contributor to overall satisfaction with their perioperative care for these young, relatively fit patients, which is consistent with satisfaction data from similar populations of patients undergoing day surgery.

In conclusion, this randomized, double-blind, placebo-controlled, clinical trial, we found that i.v. cyclizine 50 mg, administered immediately after elective Caesarean section, significantly decreased the incidence and severity of nausea and vomiting, and the need for rescue antiemetic therapy compared with i.v. dexamethasone 8 mg and placebo. It also resulted in significantly higher satisfaction with overall postoperative care and was well tolerated. The proven antiemetic efficacy of dexamethasone after epidural morphine was not observed in this study after spinal morphine.

Acknowledgements

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