Combined epidural–spinal opioid-free anaesthesia and analgesia for hysterectomy

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Postoperative nausea and vomiting (PONV) are major problems after gynaecological surgery. We studied 40 patients undergoing total abdominal hysterectomy, allocated randomly to receive opioid-free epidural–spinal anaesthesia or general anaesthesia with continuous epidural bupivacaine 15 mg h–1 or continuous bupivacaine 10 mg h–1 with epidural morphine 0.2 mg h–1, respectively, for postoperative analgesia. Nausea, vomiting, pain and bowel function were scored on 4-point scales for 3 days. Patients undergoing general anaesthesia had significantly higher nausea and vomiting scores ($P < 0.01$) but significantly lower pain scores during rest ($P < 0.05$) and mobilization ($P < 0.01$). More patients undergoing general anaesthesia received antiemetics (13 vs five; $P < 0.05$), but fewer received supplementary opioids on the ward (eight vs 16; $P < 0.05$). We conclude that opioid-free epidural–spinal anaesthesia for hysterectomy caused less PONV, but with less effective analgesia compared with general anaesthesia with postoperative continuous epidural morphine and bupivacaine.

Keywords anaesthetic techniques, epidural; anaesthetic techniques, subarachnoid; anaesthesia, general; surgery, gynaecological; vomiting, nausea; vomiting, incidence; pain, postoperative; analgesics opioid

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Postoperative nausea and vomiting (PONV) are common adverse events after anaesthesia and surgery, and patients undergoing major gynaecological surgery are especially prone to PONV, with reported incidences of 50–75%. Opioids are potent emetics as a result of direct action on receptors in the chemotriggert zone in the brainstem, and they are often used as part of a general anaesthesia regimen for postoperative analgesia. An opioid-free regional anaesthesia regimen combined with postoperative use of peripherally acting analgesics and epidural administration of local anaesthetics may be a rational approach to reduce the incidence and severity of PONV.

The purpose of this study was to investigate if a multimodal non-opioid regimen reduced the incidence of PONV compared with routine inhalation anaesthesia, with postoperative use of epidural morphine and bupivacaine.

Patients and methods

The study was approved by the Ethics Committee of Frederiksberg and Copenhagen Municipalities and patients gave oral and written informed consent.

This was an open, prospective, randomized study comparing two different anaesthetic techniques. We studied 40 ASA I and II patients undergoing total abdominal hysterectomy, allocated randomly by closed envelopes to receive combined epidural–spinal anaesthesia (group ES) or conventional isoflurane inhalation anaesthesia (group GA). Exclusion criteria were allergy or intolerance to amide-type local anaesthetics or non-steroidal anti-inflammatory drugs (NSAID), symptoms relating to or active duodenal/gastric ulcer, neuromuscular disease or hereditary disposition to malignant hyperthermia.

All patients were premedicated with midazolam 7.5 mg orally, 30–45 min before anaesthesia. In both groups an epidural catheter was inserted at the T10–11 or T11–12 intervertebral space by a paramedian technique, which was confirmed by administration of 2% lidocaine with epinephrine 3 ml +3 ml to exclude spinal anaesthesia. In group ES, hyperbaric 0.5% bupivacaine 3 ml was given intrathecaclly in the L4–5 or L3–4 intervertebral space by a median approach. Bupivacaine 0.5% (6–9 ml) was injected into the epidural catheter, followed by 6 ml h–1 for a bolus, and 8 ml h–1 (1.9 mg ml–1) for infusion. Before closure of subcutaneous tissues, 0.25% bupivacaine 15 ml was injected subfascially in each rectus muscle. No opioid
was given. In group GA, anaesthesia was induced with fentanyl 3 \(\mu\)g kg\(^{-1}\), thiopental 4 mg kg\(^{-1}\) and atracurium 0.5 mg kg\(^{-1}\). Anaesthesia was maintained with isoflurane and nitrous oxide in oxygen, supplemented if necessary by fentanyl. Neuromuscular block was antagonized with atropine 1 mg and neostigmine 2.5 mg. Before wound closure, morphine 2 mg and 0.25% bupivacaine 8 ml were injected epidurally.

In group ES, tenoxicam 40 mg was administered i.v. at the end of anaesthesia, and orally 24 h after operation. Epidural infusion of bupivacaine (1.9 mg ml\(^{-1}\)) 8 ml h\(^{-1}\) was continued for 48 h after operation. In group GA, epidural infusion of bupivacaine (2.5 mg ml\(^{-1}\)) and morphine (50 \(\mu\)g ml\(^{-1}\)) 4 ml h\(^{-1}\) was started after epidural injection at wound closure and continued for 48 h. In both groups, paracetamol 2 g was given rectally immediately after operation and orally 1 g four times a day for the next 3 days; morphine 10 mg was given for insufficient pain therapy as i.m. injections or as tablets if tolerated. A higher infusion rate with a lower concentration of bupivacaine in group ES (15 mg h\(^{-1}\) vs 10 mg h\(^{-1}\)) was used to compensate for the use of epidural morphine in group GA. Antiemetics were administered as judged necessary by the PACU and ward staff.

All patients received 6% hydroxyethyl starch (HAES) 500 ml infused before placement of the epidural catheter. Isotonic saline 10 ml kg\(^{-1}\) h\(^{-1}\) was infused as replacement for evaporation and diuresis. Blood loss was replaced by isotonic saline 500 ml and HAES 500 ml for the first 1000 ml, and thereafter by SAG-M blood, 1 ml per ml of blood loss.

Patients were asked to resume normal eating and drinking habits as soon as possible. To promote bowel function, magnesium oxide 1 g daily, cisapride 20 mg twice daily and protein drink 125 ml twice daily were given from the evening after operation. Patients were encouraged to be out of bed for 2 h on the first evening, for 8 h and at meals on day 1, and all day on day 2. The bladder catheter, placed immediately before operation, was removed 24 h after operation.

Before operation, patients were asked about previous experiences of PONV. Duration of stay in the post-anesthetic care unit (PACU), postoperative use of analgesics and antiemetics were retrieved from anesthesia files and patient records; PACU nurses administering medication could not be blinded to the anaesthetic regimen. Similarly, nurses on the ward were not blind to the anaesthetic regimen.

After thorough preoperative instruction by one of the authors (T. C.), patients completed questionnaires regarding nausea, vomiting, pain, mobilization, and bowel and bladder function. Scoring was performed every 12 h, describing the preceding 12 h for the first 72 h after operation. The questionnaires were checked daily by T. C. to ensure adequate scorings.

Nausea and pain (during rest, while coughing and rising from the supine to the sitting position) were scored on 4-point verbal rank scales (none=0, light=1, moderate=2, severe=3). The number of episodes of vomiting and number of defaecations were noted. Painful voiding or need for recatheterization of the bladder were also noted.

Descriptive statistics (median and interquartile range (IQR)) were used for patient data and for use of anaesthetics, analgesics and surgery time. Pain, nausea and vomiting scores were pooled for the six 12-h intervals, assigning the following numbers: 0=no pain/no nausea/no vomiting, 1=light pain/light nausea/one vomiting episode, 2= moderate pain/moderate nausea/two vomiting episodes and 3=severe pain/severe nausea/three or more vomiting episodes. Cumulative pain, nausea and vomiting scores (CPS, CNS and CVS, respectively) were compared using the Wilcoxon–Mann–Whitney test. Frequencies were compared using the chi-square test with Yates’ correction, and time to first defaecation was compared using the Komolgorov–Smirnov two-sample test. The level of significance was 5%. No study with nausea scores, including variability data, was available to estimate the necessary number of patients. We calculated that to detect a 50% reduction (80% to 40%) in PONV, 17 patients would be required in each group to achieve an \(\alpha\) error of 5% and a \(\beta\) error of 20%. Thus 20 patients in each group was considered sufficient.

### Results

The two groups were similar in age, height, weight, duration of surgery and duration of time in the PACU (Table 1). Eight and ten patients in group ES and group GA, respectively, had previous experience of PONV.

There were no significant differences in blood loss or amount of blood, saline or hydroxyethyl starch infused. In two patients in group ES, restlessness and anxiety, but not pain, during surgery, necessitated anaesthesia (propofol 250 mg, assisted ventilation via a laryngeal mask and propofol 1200 mg, atracurium 40 mg, intubation).

Use of opioids, antiemetics, supplementary bupivacaine and ephedrine in the PACU is shown in Table 2. Significantly fewer patients in group ES (0 vs 10) received opioids \((P<0.001)\), whereas the number receiving antiemetics was not significantly different during the stay in the PACU (0 in group ES vs five in group GA; 0.05\(<P<0.1)\).

Use of morphine and antiemetics on the ward is shown in Table 2. The number of patients requiring opioids on the

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**Table 1** Patient characteristics and surgery data (median (interquartile range)) in the combined epidural–spinal anaesthesia group (group ES) and the general anaesthesia group (group GA)

<table>
<thead>
<tr>
<th></th>
<th>Group ES ((n=20))</th>
<th>Group GA ((n=20))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>48 (43–50)</td>
<td>45 (43–48)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164 (159–167)</td>
<td>165 (162–168)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65 (56–75)</td>
<td>66 (61–70)</td>
</tr>
<tr>
<td>Surgery time (min)</td>
<td>92 (73–118)</td>
<td>85 (73–111)</td>
</tr>
<tr>
<td>Stay in PACU (min)</td>
<td>157 (120–240)</td>
<td>150 (131–163)</td>
</tr>
</tbody>
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**Table 2** Use of opioids, antiemetics, supplementary bupivacaine and ephedrine in the PACU (0=0, light=1, moderate=2, severe=3, vs 10) Group GA (n=20)

<table>
<thead>
<tr>
<th></th>
<th>Group ES ((n=20))</th>
<th>Group GA ((n=20))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of opioids</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Use of antiemetics</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Supplementary bupivacaine</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>
Table 2 Number of patients receiving supplementary analgesics and antiemetics in the post-anaesthetic care unit (PACU) and on the ward during the first 72 h after operation in the combined epidural–spinal anaesthesia group (group ES) and the general anaesthesia group (group GA)

<table>
<thead>
<tr>
<th></th>
<th>Group ES</th>
<th>Group GA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PACU</td>
<td>Ward</td>
</tr>
<tr>
<td>Morphine i.v., i.m. or oral</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Bupivacaine epidurally</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ephedrine i.v.</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Antiemetics</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

Fig 1 Time courses of nausea and vomiting. Left columns=epidural–spinal anaesthesia group; right columns=general anaesthesia group. Cumulative scores were significantly higher in the general anaesthesia group for both nausea \((P<0.01)\) and vomiting \((P<0.001)\).

Fig 2 Time course of pain at rest, on coughing and during mobilization. Left columns=epidural–spinal anaesthesia group; right columns=general anaesthesia group. Cumulative scores were significantly higher in the epidural–spinal group at rest \((P<0.05)\) and during mobilization \((P<0.001)\), but not while coughing \((P=0.36)\).

ward for the following 3 days was significantly higher in group ES than in group GA \((16 \text{ vs } 8; P<0.05)\), whereas the reverse was true for antiemetics \((5 \text{ vs } 13; P<0.05)\).

The time course of nausea and vomiting over the first 72 h is shown in Figure 1. Cumulative scores for both nausea and vomiting were significantly higher in group GA than in group ES \((P<0.002 \text{ for nausea; } P<0.0001 \text{ for vomiting})\). All patients in group GA experienced some degree of PONV during the first 72 h after operation compared with only 10 of 20 patients in group ES \((P<0.0001)\). In group ES, nine of 16 patients receiving postoperative opioids and one of four patients who did not receive opioids developed some degree of PONV (ns).

The time course of pain during rest, coughing and mobilization is shown in Figure 2. Cumulative pain scores were significantly higher in the epidural–spinal group both at rest \((P=0.026)\) and on mobilization \((P<0.001)\). On coughing, cumulative pain scores were not significantly different \((P=0.36)\).

The median time to first defaecation was interval 3 \((24–36 \text{ h})\) in group ES compared with interval 5 \((48–60 \text{ h})\) in group GA. However, the difference was not statistically significant \((P=0.1, \text{Komolgorov–Smirnov two-sample test})\).

At the end of interval 1 \((0–12 \text{ h})\), two of 20 patients in each group were walking freely; this increased to 12 of 20 patients in group ES, and 11 of 20 patients in group GA were walking freely at the end of interval 6 \((60–72 \text{ h})\) (no significant differences at any time).

In group ES, three patients had incisional haematomas requiring surgical intervention, and one patient had a haematoma at the vaginal cuff requiring drainage. Pain scores for these patients did not differ from those of the other patients in group ES. There were no postoperative complications in group GA. No case of post-spinal puncture headache was reported.
Discussion

The relationship between PONV and several aetiological factors, including use of opioids and nitrous oxide, has been established, and PONV remains a major clinical problem, despite the development of antiemetic agents. There are no data from large scale studies comparing regional and general anaesthesia for major gynaecological surgery with respect to PONV, and information from other types of surgery is limited, but in favour of regional anaesthesia.

The main result of our study on PONV after hysterectomy was that regional anaesthesia resulted in significantly less PONV and less use of antiemetics than general anaesthesia. In comparative studies of different antiemetic regimens in general anaesthesia for major gynaecological surgery, cumulative incidences of PONV over 24–72 h of 71–89% have been reported in both treatment and control groups. The use of regional anaesthesia seems at least as effective as different pharmacological approaches to reduce PONV, as the cumulative frequencies were 50% in the regional anaesthesia group and 100% in the general anaesthesia group in our study.

Time to normal bowel function did not differ significantly between groups. A trend towards earlier return of bowel function in group ES (median 24–36 h compared with 48–60 h in group GA) is similar to that found by Thören and colleagues who compared a larger dose of continuous 0.25% epidural bupivacaine 8 ml h⁻¹ and epidural morphine (on request) for postoperative pain relief in 22 patients after hysterectomy under general anaesthesia. They found that normal bowel function returned after 57 h in the bupivacaine group compared with 92 h in the morphine group. The fact that in our study both groups received epidural bupivacaine may explain the relatively rapid recovery of bowel function in both groups.

Cumulative pain scores during rest and mobilization were significantly higher in the ‘opioid-free’ ES group, together with a more frequent use of opioid analgesics after leaving the PACU. This difference must be viewed in the light of the prolonged analgesic effects of spinal–epidural anaesthesia. Thorén and colleagues also found significantly more PONV in the epidural morphine group, but with higher pain scores than in the epidural bupivacaine group. The difference between these results and ours may be explained by the lower dose of bupivacaine in group ES (15 mg h⁻¹) and the use of combined epidural bupivacaine and morphine in group GA.

Patients’ overall ability to move was not affected by the ‘opioid-free’ regimen and a possible positive effect of less PONV was probably counter-balanced by the inferior analgesia, reflected by the higher pain scores in group ES. Neither PONV nor postoperative pain has been analysed previously with respect to functional limitation after major gynaecological surgery.

For obvious reasons, patients, surgeons, anaesthetists and nursing staff in the PACU could not be blinded and the open design indicates a possibility of bias. However, the primary purpose was to compare fundamentally different anaesthetic regimens with respect to PONV, and not the influence of a single factor, where a blinding procedure would have been easier.

In summary, we conclude that the incidence of PONV was reduced markedly, but was not eliminated when an intra- and postoperative continuous local anaesthetic regimen was compared with a general anaesthetic technique using isoflurane and fentanyl with continuous epidural bupivacaine–morphine for postoperative pain relief. However, pain relief was inferior with the opioid-free local anaesthetic regimen. As provision of opioid-free anaesthetic and analgesic regimens is rational, and as opioids are potent emetic agents with other undesirable effects in the postoperative period, further studies of multi-modal opioid-free balanced anaesthetic and analgesic regimens are required.

Acknowledgement

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References


