Cyclizine and droperidol have comparable efficacy and side effects during patient-controlled analgesia

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Abstract

**Background** Post-operative nausea and vomiting (PONV) is common, especially following gynaecological surgery. Patient-controlled analgesia (PCA) is frequently complicated by nausea. We assessed PONV, pain and sedation in patients receiving cyclizine or droperidol during PCA following abdominal hysterectomy in a double-blind trial.

**Methods** Thirty women were randomised to receive either cyclizine 0.7mg/kg or droperidol 0.04mg/kg during surgery followed by PCA containing morphine sulphate with cyclizine 2mg or droperidol 0.05mg per demand. Blinded observers scored levels of nausea, sedation, anxiety and pain.

**Results** Pain scores, PCA usage and supplemental antiemetic requirements were comparable. Nausea and sedation scores were similar in both groups. Two patients in each group developed refractory PONV. Pre-operative anxiety scores were similar and decreased comparably over time. Patients developing refractory emetic sequelae had a higher incidence of previous PONV. Previous PONV also predicted lower PCA medication intake despite similar demand rates, suggesting increased usage during lock-out periods.

**Conclusion** Prophylactic cyclizine and droperidol have similar efficacy during PCA. Neither is associated with perioperative anxiety. A minority of patients have refractory PONV during PCA. Previous PONV may predict less efficient PCA usage.

Introduction

Systemic opioid analgesia, especially when self-administered, remains a standard of care for post-operative pain relief but is frequently associated with emetic sequelae, especially in women. The optimum methods of prevention and treatment of PONV, including opioid-associated emesis, are still unknown. In this study, we evaluated the efficacy of two antiemetics, droperidol and cyclizine, in the prevention of PONV in patients receiving self-administered intravenous morphine. We also investigated the sedation and anxiety associated with antiemetic prophylaxis during PCA use.

Patients and methods

**Patient selection**

The study protocol was approved by the Hospital Committee for Research on Human Subjects. Thirty ASA physical status 1-3 patients undergoing abdominal hysterectomy gave written informed consent to participate. Exclusion criteria included pre-operative chronic analgesic/antiemetic use or substance dependence; previous adverse reactions (other than nausea) to anaesthesia or narcotic analgesics; and neuropsychiatric illness, including history of post-operative confusional state.

**Patient allocation**

The study followed a randomised, double-blind design. All patients underwent assessment using the Spielberger State Trait Anxiety Inventory and received instruction in assessment of pain by visual analogue scale (VAS). During surgery, each was randomly assigned to receive intraoperative prophylaxis using either cyclizine 0.07mg/kg (group I) or droperidol 0.04mg/kg (group II) administered intravenously 20 minutes before abdominal wound closure, followed by post-operative prophylaxis with cyclizine or droperidol added to PCA in the ratio of 2mg or 0.05mg per mg of morphine administered, respectively.

**Pre-operative management and anaesthesia**

Patients received premedication with oral diazepam 7.5-10mg one hour before surgery. Anaesthesia was induced in all patients with fentanyl (1-1.5µg/kg) and propofol (1.5-2mg/kg), and maintained using isoflurane-nitrous oxide oxygen. Muscle relaxation was maintained with vecuronium. All patients received intravenous morphine sulphate (0.15mg/kg) 10 minutes prior to surgical incision. At completion of surgery, neuromuscular blockade was reversed with neostigmine-glycopyrrolate, patients’ tracheas were extubated and they were transferred to the PACU.

Following PACU admission, intravenous morphine sulphate was permitted in both groups for early post-operative analgesia until patients were considered capable of using a PCA infusion device (AP II Infuser, Abbott, Chicago) programmed to deliver intravenous morphine sulphate (1.0mg bolus) with a six-minute lock-out period and a four-hour maximum dose of 30mg, without background infusion. Pain was assessed using a 10cm VAS with zero and 10 labelled as ‘no pain’ and ‘worst pain imaginable’, respectively. Resting VAS scores were obtained on PACU arrival and repeated 4, 24 and 48 hours postoperatively. No other analgesic agents were used. Nausea or vomiting were treated with intramuscular promethazine 12.5mg; patients with refractory emetic problems received intravenous ondansetron 4mg. Severe nausea or vomiting despite prophylaxis and treatment mandated discontinuation of PCA.

**Post-operative assessment**

Patients were assessed for 48 hours by a blinded research observer who
performed repeat scoring of the state component of STAI (STAI-S) and elicited pain and sedation scores. Adverse effects (pruritus, nausea, subjective complaints of excessive sedation) were recorded if present. Severity of nausea was graded using a five-point ordinal scale (1=nil, 2=mild nausea, 3=moderate nausea, 4=severe nausea, 5=active vomiting). Sedation was scored using the Trieger dot test and the portable mini mental state test.

Withdrawal of patients
Withdrawal criteria included failure of surgery to proceed as planned or development of post-operative complications limiting assessment. Refractory emesis was considered to be both a study endpoint and a withdrawal criterion. Data collected up to the time of discontinuation were retained for analysis.

Statistical analysis
Prior to study commencement, sample size calculations were performed. Our sample size calculations were based on pilot STAI-S scores of 40±10 (mean±SD). As we anticipated a possible increase in STAI-S associated with droperidol relative to patients receiving cyclizine, we calculated a sample size so that a between-group mean difference (D) in post-operative STAI-S scores of 10, with higher STAI-S scores in group II, would permit a type I error rate of one tailed \( \alpha =0.05 \) with a type II error of \( \beta =0.20 \), i.e. power equal to 0.80. Using the formula for deriving sample size (n), we estimated that a total sample size n=26 would be required.

Demographic data were analysed using Student’s t-test or Fisher’s exact test as appropriate. Sedation and nausea scores and PCA consumption were compared using the Mann-Whitney U test. Mini mental state and VAS pain scores were analysed by repeated measures ANOVA with group as the between-group factor and time after surgery as the repeated measures factor. The Student-Newman-Keuls test was used for multiple comparison testing. Continuous data were presented as means±standard error of the mean (SEM) or medians±interquartile range (Q1-Q3) as appropriate; categorical data were presented as frequencies. The null hypothesis was rejected at the 0.05 probability level.

Results
Demographic and surgical variables
The two groups were demographically comparable and had similar pre-operative STAI-T scores and post-operative PCA usage (see Table 1). PACU pain scores and morphine requirements were similar. PCA utilisation (both demands and delivered) were similar over the 48-hour study period. PCA usage differed between patients who had a positive or negative history of PONV. While demand patterns were identical (111 [21] demands vs 118 [11] demands, respectively; p=0.05), patients with a previous history of PONV obtained significantly smaller amounts of morphine (62 [7] mg vs 90 [10] mg; p<0.03) despite having similar pain scores (data not shown).

Post-operative period
Nausea and VAS pain scores were comparable in groups I and II (see Figures 1 and 2). The incidences of severe nausea and vomiting were low and comparable (p>0.5) at all times (data not shown). Three patients in each group required supplemental antiemetics; four (two per group) also received third line treatment. Despite rescue antiemetics, these latter patients all developed refractory PONV mandating discontinuation of PCA. Patients developing refractory PONV did not differ demographically from those who did not, but had a higher incidence of previous PONV (4 of 4 vs 11 of 26, p=0.05). No overt dysphoria or extrapyramidal symptoms occurred. STAI-S scores decreased over time (p<0.001) to a similar extent in each group (see Figure 3). Mini mental state scores were decreased at four hours relative to baseline and later post-operative scores (p<0.0001) but were comparable in both groups throughout (see Figure 4). Trieger dot test scores did not differ between groups at any time points (see Figure 5).

Table 1. Patient demographics and surgical characteristics

<table>
<thead>
<tr>
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<th>Group I (n=14)</th>
<th>Group II (n=16)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>46 (2)</td>
<td>44 (3)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68 (3)</td>
<td>67 (3)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>86 (6)</td>
<td>83 (7)</td>
</tr>
<tr>
<td>STAI (trait)</td>
<td>37 (2)</td>
<td>38 (3)</td>
</tr>
<tr>
<td>Previous PONV (Y/N)</td>
<td>8/6</td>
<td>7/9</td>
</tr>
<tr>
<td>PACU morphine (mg)</td>
<td>0.4 (0.4)</td>
<td>1.9 (1.0)</td>
</tr>
<tr>
<td>PCA attempts</td>
<td>123 (27)</td>
<td>109 (12)</td>
</tr>
<tr>
<td>PCA consumption (mg)</td>
<td>86 (12)</td>
<td>68 (6)</td>
</tr>
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Data are means (SEM) or frequencies. STAI, Spielberger state trait anxiety inventory; PONV, post-operative nausea and vomiting; PACU, post-anaesthesia care unit; PCA, patient-controlled analgesia.
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Discussion

In this study, morphine-based PCA supplemented with droperidol or cyclizine was associated with a relatively low incidence of nausea or supplemental antiemetic requirement. There was no difference in PCA usage. Patient sedation, psychomotor performance and anxiety levels were similar with both antiemetic agents.

Prophylactic antiemetic use is attractive in patients with known high risk of PONV. This is especially so where post-operative opioid use is likely to be required. Despite being common and having multiple well-documented predisposing factors, the prophylaxis and management of post-operative emesis is often suboptimal. This may be related to deficiencies in the knowledge or attitudes of caregivers, but also to the sporadic nature of PONV in many patients. For example, while a multivariate prediction system incorporating female gender, opioids and previous PONV had a predictive value of 71%, its sensitivity was approximately 40%. Ongoing prophylaxis, using either scheduled bolus doses or incorporating antiemetic agents into PCA infusions, may represent an advance, but data on this practice remain limited. Prophylactic antiemetic use is attractive in patients with known high risk of PONV. This is especially so where post-operative opioid use is likely to be required. Despite being common and having multiple well-documented predisposing factors, the prophylaxis and management of post-operative emesis is often suboptimal. This may be related to deficiencies in the knowledge or attitudes of caregivers, but also to the sporadic nature of PONV in many patients. For example, while a multivariate prediction system incorporating female gender, opioids and previous PONV had a predictive value of 71%, its sensitivity was approximately 40%. Ongoing prophylaxis, using either scheduled bolus doses or incorporating antiemetic agents into PCA infusions, may represent an advance, but data on this practice remain limited. Available information so far suggests that the addition of droperidol to PCA results in a significant reduction in emetic sequelae. A meta-analysis has demonstrated significant benefit from droperidol added to PCA with a reduction of 50% or more in PCA-associated emetic sequelae relative to control. With a ‘number needed to treat’ value of 3 we felt unable for ethical reasons to use placebo controls, electing instead to compare the efficacy and side effects of droperidol with an alternative agent. Our findings confirm and extend those of Walder and Aitkenhead who demonstrated comparable efficacy for cyclizine and droperidol.

At least half the study patients reported the absence of nausea at all time intervals, while up to 25% of patients complained of at least mild nausea despite prophylaxis, especially in the first 24 hours. In a minority, severe PONV persisted despite both prophylaxis and maximum medical treatment, leading to discontinuation of PCA. A positive previous history may predict a higher probability of nonresponse to antiemetic prophylaxis, but is of limited utility in isolation, as such histories were common even in patients that had no subsequent emetic problems.

The difference in PCA usage in relation to previous emetic history was surprising and the reason for it uncertain. The lower delivery/demand ratio in these patients implies that they were requesting additional PCA medication within the preset lock-out period. As their pain and nausea scores were similar to those patients with no previous emetic history, the motivation for this is not clear. It may be that they were deliberately trying to self-administer prophylactic antiemetic. Whatever the reason, it suggests that patients with previous emetic problems may use PCA devices less effectively, with higher demand/delivery ratios than their peers, despite pre-operative education. It has been demonstrated that patients receiving more detailed pre-operative instruction in PCA use have higher demand rates for antiemetic treatment, with similar PCA usage. We anticipated that droperidol prophylaxis might be associated with increased STAI scores, since even low dose droperidol has been associated with post-operative dysphoria in a day care setting, and we felt that anxiety would be best scored quantitatively, using a validated numeric system such as STAI-S. Our failure to detect evidence of subclinical dysphoria suggests that at the doses used this problem is also a sporadic one with a low incidence. Unlike its therapeutic efficacy, ‘minor adverse effects’ of droperidol appear to be dose-related, and appear at doses exceeding 4-6mg/day, a dose considerably higher than that employed here. Extrapyramidal side effects occur with a 95% upper confidence limit of 0.56%, a frequency which would be undetectable by our study. Anxiety levels
decreased significantly over time in both groups, suggesting that in the dosage used (mean self-administered droperidol intake of 3.4mg over 48 hours), in patients receiving concurrent opioid therapy; this is not a frequent problem. This is consistent with the findings of Walder, in which a non-significant incidence of clinical anxiety was reported using a similar regimen. Finally, although the lack of a placebo control group implies that the intrinsic effects of both drugs could not be examined fully, the progressive decrease in anxiety and transient sedative effects observed relative to baseline values both suggest that clinically significant dysphoria or sedation is uncommon with either regimen.

We conclude that in patients undergoing abdominal hysterectomy, prophylactic cyclizine and droperidol have comparable antiemetic efficacy during PCA and are associated with similar levels of analgesia and PCA utilisation. Patient-reported indices of sedation and anxiety are similar for each agent, with a significant, parallel decrease in anxiety over time. A significant minority of patients develop severe refractory PONV despite both prophylaxis and therapy. Since post-operative opioid use is one of the few modifiable risk factors for PONV, a previous positive history followed by the occurrence of early postoperative PONV despite prophylaxis may warrant consideration of alternative, non-opioid analgesic modalities. Finally, even when antiemetic prophylaxis is effective, patients with positive emetic histories may use PCA less efficiently.

References


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