Comparison of the Effect of Epidural Morphine and Oxycodone for Postoperative Analgesia in Patients following Major Abdominal Surgery

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Objectives: To compare the effect of epidural morphine versus epidural oxycodone on postoperative analgesia in patients following abdominal surgery on VAS scores both at rest and on coughing, the need for rescue dosing, the hemodynamic stability, adverse effects, as well as its cost in patients following major abdominal surgery.

Methods: Forty-five ASA 1-2 patients were included in this randomized, prospective, double-blinded study. Patients were allocated into two groups: Group M received 2mg morphine via epidural as bolus at the end of the surgery, then an infusion of 200ug/hr for 24 hours; and Group O received 5mg oxycodone as bolus at the end of the surgery, then an infusion of 500ug/hr for 24 hours.

Results: Patients in both groups were comparable in terms of VAS scores at rest and on coughing, need for rescue analgesics, and hemodynamic stability. Incidence of pruritus was significantly greater in Group M (P value < 0.04). Patients in Group O had significantly higher costs than in Group M (P value <0.0001).

Conclusion: Epidural morphine and epidural oxycodone used for postoperative analgesia are comparable in terms of pain scores at rest and on coughing, need for rescue analgesics, and hemodynamic stability in patients who had abdominal surgeries. The incidence of adverse effects was similar in both groups, except for pruritus which was significantly higher in patients who received epidural morphine. The cost of using epidural oxycodone was significantly higher as compared to epidural morphine.

Key words: morphine, oxycodone, epidural analgesia

INTRODUCTION

Postoperative pain, especially when poorly controlled, results in harmful acute effects and chronic effects. Approximately 75% of patients with abdominal surgery experience significant postoperative pain, and approximately 40% of these patients complain of insufficient relief with conventional pain treatment.1

Control of postoperative pain is a multimodal strategy, and epidural anesthesia plays an integral part because of the superior analgesia and physiologic benefits it provides. The use of epidural catheter is a safe and effective method for management of pain in the immediate postoperative period and meta-analysis shows that it provides superior analgesia compared with systemic opioids, with other advantages such as facilitated return of gastrointestinal function and decrease in the incidence of pulmonary complications, coagulation-related adverse events, and possibly cardiovascular events, especially in higher-risk patients or procedures.1

Objective

The objective of this study was to compare the effect of epidural morphine versus epidural oxycodone on postoperative analgesia in patients following
abdominal surgery. It aimed to compare the VAS scores of patients in the two groups both at rest and on coughing, the need for rescue dosing, the hemodynamic stability, adverse effects, as well as its costs.

METHODS

After approval by the Technical Research Board and upon obtaining informed consent, 45 ASA physical status I-II patients aged 18-65 years old scheduled for abdominal surgery were included in this double-blind, prospective, randomized control study. Patients with allergy to local anesthetics, opioids and study drugs, and patients with contraindication to regional anesthesia were excluded from the study.

Patients were given ranitidine 50mg intravenously two hours prior to the procedure and diphenhydramine 50mg intramuscularly 30 minutes prior to the procedure. Upon arrival in the operating room, non-invasive BP monitoring, ECG and pulse oximetry were hooked to the patient, and were monitored at five-minute intervals during the operation.

For patients who underwent lower abdominal surgery, continuous lumbar epidural anesthesia was used: oxygenation was via nasal cannula at 2lpm. Patient was preloaded using 10-15ml/kg of Lactated Ringer’s solution. Midazolam 1.5mg intravenously was given prior to insertion of epidural catheter. Epidural anesthesia was performed with the patient in the lateral decubitus position. Touhy needle G18 was inserted midline at the appropriate interspace for the procedure, and after loss of resistance technique, a test dose (lidocaine 60mg with epinephrine 15mg via EC) was given to check for accidental intrathecal or intravascular injection. Patient was then placed in the supine position and was given bupivacaine isobaric 0.5% 5ml at five-minute intervals until the desired block height (1-2ml/segment) is achieved. The sensory level was assessed using pinprick and cold alcohol swab along the midclavicular line bilaterally. The motor block was assessed according to the modified Bromage scale. Surgery started desired block height was achieved.

For patients who underwent upper abdominal surgery or procedures with patient positioning other than supine, a combination of general anesthesia and continuous epidural anesthesia technique was used. The same procedure for performing the epidural anesthesia was used. General anesthesia was induced with fentanyl 1-2 mg/kg IV, propofol 1.5-2.5 mg/kg IV, and rocuronium 0.6-1.2mg/kg IV. After which, tracheal intubation was done. After securing the endotracheal tube, and positioning the patient, epidural anesthesia was activated using bupivacaine isobaric 0.5% at 1-2ml/segment up to the desired block height. Anesthesia was then maintained with isoflurane at low MAC and oxygen.

Patients were divided into two groups using the table of random numbers: Group M received 2mg morphine via epidural as bolus at the end of the surgery, then and infusion of 200ug/hr for 24hours; and Group O received 5mg oxycodone as bolus at the end of the surgery, then and infusion of 500ug/hr for 24hours. The patient who received the study drug, the anesthesiologist who administered the study drug and the nurse or anesthesiologist assigned for monitoring the patient postoperatively was blinded to the study drug used.

Patients were monitored every 30min from the end of the surgery up to 3hours post-operatively, then every hour thereafter up to 24hours. Patients stayed at the Post-Anesthesia Care Unit (PACU) for 24hours after the end of surgery. The intensity of pain at rest and on coughing was assessed using a standard Visual Analog Scale (VAS). Ketorolac 30mg IV was given as a rescue analgesic when the patient complained of a VAS score of 5 or greater, or as requested by the patient.

Patients were also monitored for the adverse effects usually seen with opioids. Blood pressure was monitored every 15minutes using a non-invasive BP. Sedation level was monitored using the Bedside Sedation Scale for Evaluation of Respiratory Depression (0=alert, 1=occasionally drowsy, easily aroused, 2=frequently drowsy, easily aroused, 3=somnolent, difficult to arouse, S=normal sleep, easily aroused). Respiratory rate was also monitored at regular intervals. Other side effects, such as nausea and vomiting, pruritus, and urinary retention were monitored. The observer in the PACU was instructed
to administer the following drugs in the presence of adverse events: ephedrine 5-10mg IV bolus once the patient had an episode of hypotension (defined as BP $\leq$80/50mmHg), naloxone, 0.08mg IV every 2min as needed for a sedation level of 3 or RR of $\leq$8 breaths/min, nausea and vomiting with metoclopramide 10mg IV every 8hours as needed, and pruritus with diphenhydramine 25mg IV every 6hours as needed.\(^2\)

**Statistical Analysis**

Sample size computation using power analysis required at least 46 patients per group to detect a clinically significant difference among the two groups. Statistical analysis was done using SPSS version 10 for windows. Descriptive statistics were generated for all variables. For nominal data, frequencies and percentages were computed. For numerical data, mean $\pm$ SD were generated. Analysis of the different variables was done using the following test statistics: T-test to compare two groups with numerical data, Mann Whitney U test for non-parametric data, Chi-square test to compare nominal data, and Fisher exact test. Significance was pegged at the 0.05 level.

**Limitation**

Due to time and financial constraints, the sample size was lower than the one computed, thus decreasing the power of this study. The study was also done by different anesthesiologists and observers, thus factors affecting the epidural anesthesia and interindividual differences in assessment were not controlled in this study.

**RESULTS**

Of the 45 patients enrolled in the study, 22 patients received morphine epidural infusion, while the other 22 received oxycodone infusion. One patient was dropped from of the study because of failed epidural catheter insertion.

Table 1 shows the comparison of the demographic characteristics of subjects between the two groups. The results showed that there was no significant difference in the different demographic characteristics as proven by all P values $>0.05$.

**Table 1. Comparison of the demographic characteristics between the two groups.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years) $\pm$ SD</th>
<th>Sex</th>
<th>Weight $\pm$ SD</th>
<th>ASA Class</th>
<th>Abdominal Surgery</th>
<th>Duration of Surgery (min)</th>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>46.32 $\pm$ 7.90</td>
<td></td>
<td>55.50 $\pm$ 7.64</td>
<td>12 (54.5%)</td>
<td>17 (77.3%)</td>
<td>186.59 $\pm$ 56.30</td>
<td>CLEA</td>
</tr>
<tr>
<td>Group</td>
<td>46.59 $\pm$ 10.15</td>
<td></td>
<td>57.09 $\pm$ 9.77</td>
<td>10 (45.5%)</td>
<td>14 (63.6%)</td>
<td>185.22 $\pm$ 76.13</td>
<td>GA-Epidural</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female 18 (81.8%)</td>
<td>Male 4 (18.2%)</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>17 (77.3%)</td>
<td>5 (22.7%)</td>
<td>2</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 (54.5%)</td>
<td>10 (45.5%)</td>
<td>Lower</td>
<td>17 (77.3%)</td>
<td>16 (72.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>14 (63.6%)</td>
<td>8 (36.4%)</td>
<td>Upper</td>
<td>5 (22.7%)</td>
<td>6 (27.3%)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1 shows the VAS scores of patients at rest among the two groups. The results show no statistical difference, with a P value of $>0.05$.

Figure 2 shows the VAS scores of patients on coughing between the two groups. There was no significant difference among the two groups.

Figures 3-6 show the heart rate, mean arterial pressure, respiratory rate, and sedation level of Group
M and Group O. All results show that there is no statistically significant difference among the vital signs of the two groups.

Table 2 shows the number of times the patient asked for rescue doses of ketorolac during the first 24 hours post-op. Some of the patients in both groups received rescue doses, but the difference is not clinically significant.

Table 3 shows the adverse effects experienced by the patients by the two groups. Results show that there were six patients who experienced nausea and vomiting in Group M while there were only two in group O, but statistical data suggest that it is not clinically significant. No patient experienced pruritus in Group O but there were five patients who experienced pruritus in Group M, which was statistically significant, with a P value of 0.04.

Table 4 shows the comparison of costs between the two groups. The total cost in Group O was significantly higher than in Group O, with a P value of <0.0001.

DISCUSSION

This present study shows that epidural morphine and epidural oxycodone used for postoperative
analgesia are comparable in terms of pain scores at rest and on coughing, hemodynamic stability, and adverse effects, except for pruritus, which was significantly greater in patients receiving epidural morphine. The cost of using oxycodone was significantly higher, compared with that of morphine.

Table 3. Comparison of adverse effects between the two groups.

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Group M</th>
<th>Group O</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Respiratory depression / excessive sedation</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>6 (27.3%)</td>
<td>2 (9.1%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5 (22.7%)</td>
<td>0</td>
<td>0.04</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
</tbody>
</table>

Table 4. Comparison of total cost between the two groups.

<table>
<thead>
<tr>
<th>Total Cost</th>
<th>Group M</th>
<th>Group O</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>15</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>101 - 200</td>
<td>6</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>201 - 400</td>
<td>1</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>401 - 600</td>
<td>0</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>601 - 800</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Morphine is the prototype opioid and was the “gold standard” to which all other analgesics are compared. It is primarily metabolized in the liver by conjugation to form water-soluble metabolites, morphine-3 and morphine-6-glucopronides, of which morphine-6-glucoronide is said to be potent analgesic. Morphine given via the epidural route provides excellent postoperative analgesia, but the incidence of side effects such as nausea, vomiting, pruritus, respiratory depression, and urinary retention limits its use.3

Oxycodone, a thebaine derivative, resembles morphine in structure and lipid solubility.4 It is a full opioid agonist with no antagonistic properties whose principal therapeutic action is analgesia. Like morphine, it has two metabolites, noroxycodone and oxymorphone, both of which have potent analgesic effects. When given through the intravenous route, its analgesic onset is faster as compared with morphine, and with less incidence of side effects.5,4 Studies on the use of oxycodone in the epidural route has been very limited.

The analgesic potency ratio between morphine and oxycodone was 3:2 when given in intermittent IV blousing, making IV oxycodone more potent than IV morphine. Backlund, et al. in 1997 first studied the effect of epidural oxycodone as compared with epidural morphine, and concluded that an epidural dose ratio between morphine and oxycodone via infusion was 1:9.8 whereas for total consumption it was 1:8.4. Chizuko, et al. in 2000 also compared epidural morphine and oxycodone via bolus or continuous administration for postoperative pain and nausea after gynecological surgery in a 1:2.5 ratio, and results showed that there was no significant difference in the pain scores in both groups, with significantly less incidence of nausea in patients who received epidural oxycodone.5 Yanagidate and Dohi in 2004 similarly studied the effect of epidural oxycodone as compared to epidural morphine and they concluded that epidural oxycodone is as effective as morphine when given twice the dose, perhaps with fewer side effects.6

The differences in efficacy ratio of epidural morphine and oxycodone may be accounted for by their differences in 1) affinity for opioid receptors, 2) analgesic potency of their metabolites, and 3) presence of supraspinal action.

Both morphine and oxycodone have m-receptor affinity, but the affinity of oxycodone for the m-opioid receptor is said to be one-tenth that of morphine.6 Recent studies by Ross, et al. have also shown that the intrinsic antinociceptive effects of oxycodone are mediated by k-opioid receptors in contrast to morphine which interacts primarily with μ-opioid receptors.7

Morphine-6-glucuronide, one of the metabolites of morphine is said to be responsible for the majority
of the analgesic property of morphine. Binding of this metabolite to m-opioid receptors is comparable with that of morphine, but its analgesic potency is 650-fold that of morphine.\(^8\) Oxycodone has two metabolites, oxymorphone and noroxymorphone, both of which have unclear roles in the antinociceptive effect of oxycodone. In pilot experiments of Backlund, et al. no oxymorphone in plasma was found during epidural infusion.\(^4\) Lalovic, et al. studied the effect of the circulating metabolites of oxycodone and results showed that the central opioid effects of oxycodone are governed by the parent drug, with a negligible contribution from its circulating oxidative and reductive metabolites.\(^9\) Poyhia, et al. also failed to find oxymorphone in plasma after IV administration of oxycodone, hence its role as an analgesic is probably negligible.\(^4\) Noroxymorphone, another metabolite of oxycodone, according to a study by Lemberg, et al. has a negligible role when given via the systemic route but was shown to be as efficient and potent as morphine, and with a significantly longer analgesic effect when given intrathecally.\(^10\)

Yanagidate, et al. in their study found that the reduced potency and individual variability observed in patients who received oxycodone might be attributable to the lack of supraspinal action.\(^6\) The effect of epidural oxycodone, according to Backlund, et al. is probably due to a systemic opioid effect, given the fact that the plasma concentrations and pain scores of oxycodone after both epidural and intravenous routes were almost similar.\(^4\)

In this present study, the epidural dose ratio between morphine and oxycodone was set at 1:2.5, similar to the study by Chikuzo, et al. There was no significant difference between the pain scores of the two groups, both at rest and on coughing. Hemodynamic variables such as heart rate, mean arterial pressure, respiratory rate and level of sedation are similar in both groups.

Need for rescue dosing with Ketorolac for both groups were not significantly different. This result is consistent with the study by Backlund, et al. where not complete but adequate analgesia was achieved with the opioids.

Occurrence of nausea, pruritus, respiratory depression, and degree of sedation was similar in patients who received intravenous and epidural oxycodone and epidural morphine, based on the study by Backlund, et al.\(^4\) In contrast, in the studies by Yanagidate et al and Chikuzo, et al. the patients who received epidural oxycodone had lesser incidence of nausea, a plausible explanation would be that oxycodone when administered in the epidural space, is less emetogenic than morphine.\(^5,6\) Incidence of pruritus was similar in both groups based on the study of Yanagidate, et al.

Adverse effects common to epidural opioids, most commonly nausea and vomiting and pruritus are believed to be caused by m-opioid receptor stimulation at the supraspinal level.\(^6\) As mentioned earlier, oxycodone exerts its effects at k-opioid receptors, with effects at m-receptors reported to be one-tenth that of morphine, probably accounting for the lesser incidence of side effects seen in the patients included in the study of Yanagidate, et al.\(^6\)

In our study, there was no report of respiratory depression and excessive sedation. There were more patients who experienced nausea and vomiting in Group M as compared to Group O, but this was not statistically significant. Five out of the 22 patients in Group M experienced pruritus and was given diphenhydramine 25mg intravenously. No one experienced pruritus in Group O. This result was statistically significant. A probable explanation for the lack of pruritus in this patient was the lack of histamine release of oxycodone when given in different routes.\(^3\) The lower dose of epidural oxycodone given in this study compared to that given by Backlund, et al. could be the reason for the absence of respiratory depression and excessive sedation in our patients.

In terms of cost, cost of using oxycodone was significantly higher as compared to morphine, even when the medications used for the adverse events were already accounted. This may limit the use of this drug for use via the epidural route.
CONCLUSION

In conclusion, epidural morphine and epidural oxycodone used for postoperative analgesia are comparable in terms of pain scores at rest and on coughing, need for rescue analgesics, and hemodynamic stability in patients who had abdominal surgeries. The incidence of adverse effects was similar in both groups, except for pruritus which was significantly higher in patients who received epidural morphine. The cost of using epidural oxycodone was significantly higher as compared to epidural morphine.

RECOMMENDATION

It is recommended that further studies on the optimal dosing of epidural oxycodone be made, with larger number of subjects and extended duration for postoperative analgesia. Inclusion of patient satisfaction and cost-effective analysis as parameters in future studies is also recommended.

REFERENCES


