EFFECT OF PREOPERATIVE INTRAVENOUS OXYCODONE ON LOW-DOSE ROPIVACAINE SPINAL ANESTHESIA COMBINED WITH INTRATECAL FENTANYL

Na Wang*, Songling Zhang**, Yaowen Fu*** and Jinguo Wang****

Background: Low-dose ropivacaine combined with intrathecal fentanyl can provide adequate anesthesia with minimal haemodynamic variation. Preemptive analgesia can enhance analgesic effect of spinal anaesthesia without obvious side effects.

Aims: To assess the efficacy of preoperative intravenous oxycodone on transurethral resection of prostate (TURP) under 10 mg ropivacaine spinal anaesthesia combined with intrathecal 25 μg fentanyl.

Methods: Sixty patients undergoing TURP were randomly divided into two groups: Group O (n=30), in which the patients were administered 0.1 mg·kg⁻¹ oxycodone intravenously 10 min prior to the operation for 2 min, and Group C (n=30) in which the patients were administered intravenously a similar volume of 0.9% saline. The participants were injected with hyperbaric 10 mg ropivacaine and 25 μg fentanyl intrathecally. The block characteristics, hemodynamic values, the tramadol consumption and adverse effects were analyzed.

Results: The peak level of sensory block was lower in Group C. Time to the first analgesic request and time to two-segment regression of sensory block were shorter in Group C. Fewer patients in Group O were given postoperative analgesics.

Conclusion: Preoperative intravenous oxycodone can prolong analgesic effect of this method and postoperative analgesia.

Keywords: Preemptive analgesia; Spinal anaesthesia; Oxycodone; Ropivacaine; Fenanyl

Introduction

Intrathecal anesthesia which can maintain patients awake during the surgery to detect early symptom of transurethral resection syndrome is a widely used anesthetic method for transurethral resection of the prostate (TURP). Hyperbaric 10 mg ropivacaine plus intrathecal 25 μg fentanyl can yield an adequate anesthetic condition for TURP, restrict the spread of the sensory block, and provide a rapid regain of motor function, but may not produce a satisfactory postoperative

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Preemptive analgesia can not only prolong the duration of spinal analgesia, but also improve the quality it produced, without causing an increase in the incidence of side effects. Preemptive analgesia is defined as an antinociceptive treatment that prevents the establishment of central sensitization, which amplifies pain.

Previous researches reveal that preoperative oral oxycodone can reduce intraoperative stress reaction, postoperative pain and analgesic requirements in patients under general anesthesia without an increase of side effects. So far, no studies have been found associated with the preemptive analgesia of preoperative oxycodone on ropivacaine-fentanyl spinal anesthesia.

We designed this clinical research to test the hypothesis that preoperative oxycodone could enhance ropivacaine-fentanyl spinal anesthesia in patients undergoing TURP.

**Methods and materials**

The International Clinical Trials Registry number of this clinic trial is ChiCTR-IPR-15006998. After approval of the Institutional Ethics Committee (NO. 2014-271) and obtaining written informed consent from all of the patients, 60 patients with American Society of Anesthesiologists (ASA) I to II undergoing elective TURP were recruited for this study. Patients having histories of substance abuse, mental disturbance and neurological disease, and allergic reactions to opioids were excluded from the clinical trial. With a sequence of numbers generated by computers and sealed envelopes, we divided the patients into two groups: Group O and Group C with 30 patients in each group. The study drug solution was prepared before spinal puncture. The anesthetist was unaware of the grouping situation.

Electrocardiogram, noninvasive blood pressure and oxygen oximeter were monitored. Venous access was obtained with a 16 gauge cannula. Before spinal injection, all patients received 5 ml·kg⁻¹ normal saline over 20 min. In order to prevent fluid overload resulting from absorption of irrigation fluid, the intravenous infusion was kept under minimal maintenance during the surgery.

All patients received ropivacaine 1.0 ml (10 mg) (Naropin, AstraZeneca AB, Sodertalje, Sweden), fentanyl 0.5 ml (25 µg) (Fentanyl, Yichang Humanwell Pharmaceutical CO, LTD, Yichang, China) and 10 % glucose 0.5 ml (Keli, Sichuan Kelun Pharmaceutical CO, LTD, Chengdu, China)—in total, hyperbaric ropivacaine 0.5% (2 ml) intrathecally. Intrathecal puncture was implemented at L3-4 using a 22 G Quincke needle. After spinal puncture was successful, the patients was administered intrathecally with the drug solution for 10 s with the needle bevel cephalad orientating. Then all patients were placed in a supine position with head tilted up 30°. Ten minutes after spinal injection, 0.1 mg·kg⁻¹ oxycodone (oxycodone, HAMOL LIMITED, Nottingham, U.K.) diluted with 0.9% saline to achieve a concentration of 1 mg·ml⁻¹ was given intravenously slowly for 2 min in Group O. or 0.1 ml·kg⁻¹ normal saline as placebo was administrated intravenously for 2 min in Group C. The operation began 10 min later. Mean arterial pressure (MAP) and heart rate (HR) were measured every 5 min. A bolus of 5 mg ephedrine which could be repeated every 3 min was used for treatment of hypotension defined as a reduction of more than 20 percent from the basic systolic blood pressure. Intravenous 0.5 mg atropine was used for the treatment of bradycardia which was defined as heart rate <45 beat per minute. The patients given ephedrine or atropine were recorded. Supplemental 100 µg fentanyl was given intravenously, once the patient felt pain. If another dose of fentanyl was needed, the induction of general anesthesia was performed and the patient was removed from this research. The patients were observed for the first postoperative 24 h.

The sensory block level was defined as the dermatomal segment without pain perception using a pin-prick test on both sides of the midthoracic line. The sensory block level was checked every 2 min till the peak level was achieved, and then every 10 min. The peak sensory block level was defined as the same block level which persisted for four consecutive tests. The degree of the motor block was measured using a Bromage scale which was graded as following: 1, complete motor block; 2, almost complete motor block: able only to move the feet; 3, partial motor block; 4, detectable weakness of hip flexion; 5, no detectable weakness of hip flexion; 6, no weakness at all.
The sedation score was assessed by an independent investigator using Ramsay sedation scale (1, anxious and agitated; 2, cooperative and tranquil; 3, drowsy but responds to command; 4, asleep but responds to tactile stimulation; and 5, asleep and no response). In the postoperative period, the surgeon would prescribe tramadol to the patient who declared his pain score was more than three. The participants who required tramadol, tramadol doses used and unwanted events were recorded in the first postoperative 24 h.

The time to the first analgesic request defined as the time period from the extubation of the patient to the time point when the first analgesic was required was the primary endpoint of this study. Presuming that preoperative intravenous oxycodone would prolong time to the first analgesic request by 30 min, 23 participants were needed in each group to discover the variance with 5% two-sided α and 10% β. Thirty patients were included in each group for possible dropouts.

The data analysis were conducted using SPSS 17.0 (SPSS Inc, Chicago, IL, USA). Inter-group differences in descriptive statistics were tested with Student’s t-test. Changes in MAP and HR at various time points within each group were analyzed using ANOVA for repeated measures. The peak sensory block and peak motor block were analyzed with Mann-Whitney U test between the two groups. Categorical data were compared using either chi-square or Fisher’s exact test. P values of <0.05 were accepted as statistically significant.

**Results**

No inter-group significant differences were found according to demographic data or surgical characteristics (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Group O (n=30)</th>
<th>Group C (n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>71.5 ±9.3</td>
<td>69.1 ±10.2</td>
<td>0.344</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.8 ±7.9</td>
<td>67.6 ±8.5</td>
<td>0.399</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.6 ±7.3</td>
<td>170.9 ±8.2</td>
<td>0.255</td>
</tr>
<tr>
<td>ASA I/ II (n)</td>
<td>11/19</td>
<td>7/23</td>
<td>0.398</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>56.7 ±17.4</td>
<td>53.3 ±15.4</td>
<td>0.426</td>
</tr>
<tr>
<td>Prostate volume (g)</td>
<td>60.2 ±16.4</td>
<td>65.7 ±14.1</td>
<td>0.169</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation and number of patients. ASA: American Society of Anesthesiologists.

<table>
<thead>
<tr>
<th></th>
<th>Group O (n=30)</th>
<th>Group C (n=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for Tramadol analgesia</td>
<td>9 (30%)</td>
<td>22 (73%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Time to first rescue (min)</td>
<td>275.2 ±61.4</td>
<td>216.3 ±51.8</td>
<td>0.010</td>
</tr>
<tr>
<td>Peak sensory block level</td>
<td>T9-10 (T7-T11)</td>
<td>T10 (T7-L1)</td>
<td>0.040</td>
</tr>
<tr>
<td>Time to peak Sensory block (min)</td>
<td>13.6 ±3.2</td>
<td>12.9 ±4.1</td>
<td>0.464</td>
</tr>
<tr>
<td>Time to two-segment regression of sensory block (min)</td>
<td>163.4 ±31.7</td>
<td>141.9 ±26.6</td>
<td>0.006</td>
</tr>
<tr>
<td>Peak motor block level</td>
<td>4 (2-5)</td>
<td>3 (1-5)</td>
<td>0.209</td>
</tr>
<tr>
<td>Time to peak motor block level (min)</td>
<td>9.8 ±3.7</td>
<td>11.2 ±4.5</td>
<td>0.193</td>
</tr>
<tr>
<td>Time to reach Bromage score six level (full recovery of motor block) (min)</td>
<td>193.3 ±41.3</td>
<td>175.6 ±59.4</td>
<td>0.185</td>
</tr>
</tbody>
</table>

Values are presented as number of patients, mean ± standard deviation, and median (range).
In the first postoperative 24 h, 9 patients in Group O (30%) vs 22 patients in Group C (73%) were given postoperative tramadol analgesia ($P=0.001$) and the time to the first analgesic request was longer in Group O ($P=0.010$). No significant difference was found between the two groups with respect to the time to peak sensory block, the peak motor block, the time to peak motor block and the time to Bromage score six. The peak sensory block was higher, and the time to two-segment regression was longer in Group O ($P=0.040$ and 0.006). The motor blockade was detected in all patients in both groups (Table 2).

MAP and HR 5 min after lying on the operating bed (T1), 5 min (T2) and 10 min (T3) after spinal anesthesia, 5 min (T4), 10 min (T5), 30 min (T6) and 60 min (T7) after oxycodone or normal saline administration were shown in Figure 1 and Figure 2. MAP and HR decreased because of spinal anesthesia within each group, but not significantly, and were comparable at each time point between the two groups.

The use of ephedrine was similar between the two groups. All patients were observed with a sedation score <3 at all time points. There were no significant differences between the two groups for the supplemental fentanyl use or any of the adverse events (Table 3). The SpO$_2$ and respiration rate were always within the normal range during the study period (93-100% for SpO$_2$ and 12-16 breath·min$^{-1}$ for respiration rate) in both groups. There was no vomit, respiratory depression perioperatively.

**Discussion**

The present study demonstrates that small-dose ropivacaine-fentanyl spinal anesthesia provides adequate anesthetic condition for TURP, but it doesn’t provide satisfactory postoperative analgesia. When the opioid addition to local anesthetics is

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Ephedrine use and side effects</th>
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<tbody>
<tr>
<td></td>
<td>Group O (n=30)</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>3(10%)</td>
</tr>
<tr>
<td>Supplemental fentanyl</td>
<td>0(0%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>3(10%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>4(13%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8(27%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2(7%)</td>
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<tr>
<td>Pruritus</td>
<td>3(10%)</td>
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</tbody>
</table>

Values are presented as mean ± standard deviation and number of patients (%).

Mean arterial pressure (MAP) at various time points. (T1, basic MAP; T2, 5 min after spinal anesthesia; T3, 10 min after spinal anesthesia; T4, 5 min after drug administration; T5, 10 min after drug administration; T6, 30 min after drug administration; T7, 60 min after drug administration)
not sufficient, another intravenous or intramuscular opioid or nonopioid drug usage may be considered to improve the anesthesia and analgesia. Therefore, in this study, preoperative intravenous oxycodone was chosen to improve the effect of spinal anesthesia. In the oxycodone group, the time to the first analgesic request is prolonged without an influence on motor block. The result of this study may attribute to blunt perception of pain in central nervous system resulting from preoperative oxycodone which is not associated with motor block. Fast recovery of motor block can contribute to fewer complications.

The role of preoperative oral oxycodone has been previously reported on general anesthesia. The advantage of controlled-release oxycodone given 1 h prior to operation is proved in laparoscopic cholecystectomy and liposuction. Konstantatos et al. do not find any analgesic benefit of preoperative controlled-release oxycodone for uterine artery embolization. The result is at variance with ours. The reason could be the late administration of oral oxycodone which was given to the patients just prior to the start of operation in their trial. Enough interval of time between drug injection and the start of operation was essential for preemptive analgesia. It takes 5 min for intravenous oxycodone to reach its peak level, so 10 min before the operation is selected as the administration time in the present research.

MAP and HR are reduced due to spinal anesthesia within each group, but not significantly and are not significantly different at every time point between the two groups. This implies that neither 10 mg ropivacaine-25 µg fentanyl spinal anesthesia nor intravenous oxycodone is associated with significant hemodynamic variation which is a major concern for elderly patients.

Fentanyl and oxycodone are both opioids and have the same side effects, among which respiratory inhibition is the most unwanted adverse events, because it is sometimes life-threatening. However respiratory depression is not found in the present trial. The incidences of postoperative nausea and vomiting, pruritus, dizziness are low in this study and have no inter-group difference. The result is in line with the previous study that oxycodone has fewer adverse effects than morphine. Intrathecal fentanyl also can result in these side effects. Pruritus is proved to be a common adverse effect of intrathecal fentanyl, but it is not an issue in this research. Maybe elderly patients are not susceptible to pruritus.

The limitations of this study are its small scale and the single type of the disease and the patients. Therefore, the protocol is not suitable for all patients.
Summary

In conclusion, preoperative intravenous oxycodone can prolong the effect of ropivacaine-fentanyl spinal anesthesia without causing an increase of side effects.

Conflict of interest: The authors have no financial conflicts of interest to disclose.

References

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