The Efficacy and Appropriate Dosage of Remifentanil as an Adjunct Sedative for Spinal Anesthesia in Elderly Patients

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INTRODUCTION

Regional anesthesia may require additional sedative or analgesics. Remifentanil provides a short and predictable duration of analgesic and sedative effect without the risk of accumulation when administered by continuous infusion, which render it a very useful agent for clinical practice.(1,2) Moreover, when titrated to the same level of sedation, remifentanil provides a smoother hemodynamic profile than propofol during regional anesthesia and its level of sedation can be easily adjusted.(3) However, similar to traditional opioids, remifentanil may cause significant respiratory depression,(4) which may limit its use in regional anesthesia.

In general, elderly patients require lower dosage in many drugs. Most studies suggest that aging increases brain sensitivity to narcotics.(5,6) Spinal anesthesia is associated with significant sedation progressively,(7) and central neuraxial anesthesia has been reported to decrease the dosage of both intravenous and inhalational anesthetics required to reach a defined level of sedation.(8,9) Therefore, reduction in remifentanil requirements as an adjunct sedative can be expected for spinal anesthesia in elderly patients.

The aim of this study was to determine the appropriate dosage and the efficacy of remifentanil as an adjunct for continuous infusion in elderly patients under spinal anesthesia.

MATERIALS & METHODS

The protocol of this study was approved by the Institutional Review Board of the Hospital. Forty-three elderly (age ≥65 years) American Society of Anesthesiologists (ASA) physical status 1 and 2 patients were enrolled after giving their written informed consents. Patients were scheduled for lower extremity surgery for about 2 hrs under spinal anesthesia. Patients were excluded from this study if they had any of the following conditions: clinically significant and severe cardiopulmonary, cerebrovascular, hepatic, renal, or endocrine disease, obesity (Body mass index >30), and history of chronic use of sedatives, antidepressants, or analgesics.
Table 1. Observer’s Assessment of Alertness/Sedation (OAA/S) Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Sedation level</th>
<th>Responsiveness</th>
<th>Speech</th>
<th>Facial expression</th>
<th>Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Alert</td>
<td>Responds readily to name</td>
<td>Normal</td>
<td>Normal</td>
<td>Clear, no ptosis</td>
</tr>
<tr>
<td>4</td>
<td>Light</td>
<td>Lethargic response to name</td>
<td>Mild slowing</td>
<td>Mild relaxation</td>
<td>Glazed or mild ptosis</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Response only after name is called loudly</td>
<td>Slurred or prominent slowing</td>
<td>Marked relaxation</td>
<td>Glazed and marked ptosis</td>
</tr>
<tr>
<td>2</td>
<td>Deep</td>
<td>Responds only after mild prodding or shaking</td>
<td>Few recognizable words</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>Deep sleep, unconscious</td>
<td>Does not respond to mild prodding or shaking</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2. Demographic data

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>8/30</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>77±6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156.0±6.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>56.7±4.6</td>
</tr>
<tr>
<td>ASA physical status 1/2</td>
<td>6/32</td>
</tr>
<tr>
<td>Block height (thoracic dermatome)</td>
<td>8±1.6</td>
</tr>
<tr>
<td>Remifentanil infusion time (min)</td>
<td>132.3±29.0</td>
</tr>
</tbody>
</table>

All values are mean±SD or number of patients.

No premedication was administered. All patients were monitored by standard limb lead electrocardiography, noninvasive blood pressure, and pulse oximetry when they arrived at the operating room. All patients received lactated Ringer’s solution or normal saline 6 ml/kg before receiving spinal anesthesia, and oxygen 3 L/min via nasal prongs throughout the procedure.

Spinal anesthesia was performed with the patient in the lateral decubitus position using a 25 gauge spinal needle inserted at the L3-4 or L4-5 intervertebral space. After successful puncture, 0.5% hyperbaric bupivacaine (Marcaine®, AstraZeneca, Sweden) was injected to a target block height of T10 after the bevel of needle directed at the cephalad position. The patient’s position was then changed to supine and the adequacy of regional block was assessed.

Vital signs such as blood pressure, heart rate, respiratory rate, and oxygen saturation using pulse oximetry (SpO₂), and the degree of sedation were assessed at 5, 10, 15, 20, and 30 min, and then every 15 min until the end of surgery. The degree of sedation was assessed by the investigator using the Observer’s Assessment of Alertness/Sedation (OAA/S) Scale (Table 1). (10)

We chose bolus dosage of 0.5 μg/kg and 3 μg/kg/hr of remifentanil infusion according to the initial five pilot studies and other clinical trials. (11) Remifentanil 0.5 μg/kg was administered 90 seconds before performing spinal anesthesia, followed by continuous infusion using infusion pump (Fresenius Vial, France) with an initial infusion rate of 3 μg/kg/hr. The infusion rate of remifentanil was titrated by steps of 0.5 μg/kg/hr at 15-minute intervals as required to achieve an adequate level of sedation (OAA/S score 4). Infusion of remifentanil was stopped at the end of surgery (last suture). The total infusion time of remifentanil and the time to return of alertness (OAA/S score 5) were measured.
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Fig. 1. Changes in blood pressure and heart rate following remifentanil infusion. SBP mean: mean systolic blood pressure, DBP mean: mean diastolic blood pressure, HR mean: mean heart rate, *, †, ‡: P<0.05 compared with control.

Safety was determined by respiratory and hemodynamic monitoring. Adverse events such as nausea, vomiting, dizziness, or pruritus were closely monitored during and after surgery. The infusion rate was titrated down if the patient displayed significant respiratory depression (respiratory rate ≤10 breaths/min, absence of respiratory effort for at least 15 seconds), oxygen desaturation (SpO2<94%), hypotension (systolic blood pressure <90 mmHg), bradycardia (heart rate <45 beats/min) or other adverse events. Adverse events were managed with ephedrine, atropine, or ondansetron if required.

A power analysis showed that 20 patients would provide a 90% power with an alpha of 0.05 based on 1000 Monte Carlo samples from the null distribution. Statistical analyses were performed using SAS Enterprise Guide 4.1. All data were expressed mean± standard deviation or the number of patients. We used analysis of variance for repeated measures and a p value less than 0.05 was considered statistically significant.

RESULTS

Thirty-eight patients were included in the analysis of data. Five patients were excluded from the study after receiving remifentanil. The reasons for withdrawal included unexpected intraoperative bleeding in one patient, inappropriate sedation in four patients and one of them experienced severe nausea and vomiting. Demographic and block characteristics are summarized in Table 2. The surgical procedures performed included 22 operations for the fracture of femur, 11 arthroplasties of the knee, and 5 operations for the fracture of tibia.

The mean infusion rate of remifentanil required to
maintain an adequate level of sedation without clinically significant adverse event was 3.07±0.79 μg/kg/hr (range, 2.0-5.5 μg/kg/hr) in elderly patients under spinal anesthesia. The time taken to return of alertness after discontinuation of remifentanil infusion was 8.6±4.3 min (range, 3-20 min).

Mean systolic and diastolic blood pressure decreased significantly at 5 and 10 min, and thereafter compared with control, mostly, due to intrathecal injection of bupivacaine. There was no additional reduction of blood pressure associated with remifentanil infusion. Heart rate decreased significantly at 45, 60, 75, 90, 105, and 120 min. However, only one patient’s heart rate was less than 45 beats/min, and the rate increased after decreasing the rate of remifentanil infusion. There was no clinically significant hemodynamic instability associated with remifentanil infusion (Fig. 1).

However, remifentanil infusion was associated with respiratory depression (Fig. 2). Respiratory depression was short in duration. Adequate respiration was restored in a median of 3 min after decreasing the rate of remifentanil infusion. The incidence of adverse events associated with remifentanil infusion are summarized in Table 3. SpO2 improved after reducing the infusion rate of remifentanil in 2 patients or increased FiO2 without reducing remifentanil infusion in another 3 patients.

**DISCUSSION**

This study identified the mean dose of remifentanil infusion required to maintain an adequate level of sedation was 3.07±0.79 μg/kg/hr, without significant hemodynamic instability or respiratory depression in elderly patients under spinal anesthesia.

Benzodiazepine or propofol are commonly used for sedation during surgery but they have no analgesic properties. Opioids produce sedation and drowsiness in addition to analgesia. There may be episodes of pain when surgery is prolonged or discomfort related to the tourniquet or positioning. In such cases, opioids may become useful. The high clearance of remifentanil
combined with its small steady-state distribution results in rapid decline in blood concentration after termination of an infusion. Therefore, remifentanil is potentially an adjunct to regional anesthesia. In addition, remifentanil may be an ideal agent for analgosedation due to its easy titratability and organ-independent metabolism. (13)

Aging increases the volume of distribution for all benzodiazepine, which effectively prolongs their elimination half-lives and propofol is more likely to cause apnea and hypotension in the elderly than in younger patients. Lauwers et al. (3) showed that recovery of alertness from low-dose propofol infusions was slower than expected and remifentanil could also be used for sedation during regional anesthesia.

Spinal anesthesia is accompanied by significant progressive sedation (8) and several studies have shown that spinal anesthesia can reduce the requirements of hypnotics or sedatives. (9, 14) Therefore, the dose requirements of remifentanil in elderly patients under spinal anesthesia may be less compared with younger patients or patients without spinal anesthesia. In a meta-analysis of nine clinical trials, an infusion rate for remifentanil of 6 µg/kg/hr has been suggested as an optimal balance between side effects and sedative effect in adult. (11) In the present study, the dose of remifentanil required in elderly patients under spinal anesthesia was 3.07 µg/kg/hr following 0.5 µg/kg of bolus dose.

Remifentanil produces sedation and drowsiness but they are sometimes inadequate in patients. Servin et al. (11) reported that 18% of patients receiving remifentanil 0.1 µg/kg/min could not reach an OAA/S score of 4. In this study, 9% of patients who received remifentanil alone could not achieve desired level of sedation and additional drugs, such as midazolam, were required.

When titrated to the same sedation level, remifentanil provided a smoother hemodynamic profile than propofol during regional anesthesia. (6) Analgesia based sedation using remifentanil allowed effective provision of optimal sedation without additional need for propofol in critically ill patients and good hemodynamic stability. (15)

In our study, remifentanil was administered before intrathecal injection of bupivacaine to reduce discomfort associated with spinal block. Therefore, the initial decrease in blood pressure may be related to intrathecal injection of bupivacaine rather than due to remifentanil, and hemodynamic stability was restored thereafter.

However, similar to traditional opioids, remifentanil may be associated with respiratory depression. Twenty-nine percent of patients in this study experienced respiratory depression during remifentanil infusion and reduction of the rate of infusion was required. The incidence of hypoventilation in remifentanil-treated patients was higher in patients over 65 years of age but was transient, resolving within minutes of discontinuing the infusion and the high incidence of apnea associated with remifentanil may be dose-related. (15, 16) Its rapid onset and offset of action mean that blood concentration can be rapidly titrated by reducing infusion rate to augment respiratory depression without compromising analgesia and patient comfort. Respiratory depression resolved within 3 minutes after decreasing remifentanil infusion rate and the sedation score of patients maintained in the present study.

Pollock et al. (7) showed the sedative effects of remifentanil were significantly related to its infusion rate. The degree of sedation correlated with remifentanil infusion rate but not for propofol. (3) The usual clinical end point corresponding to OAA/S level of 3 was not appropriate when a potent opioid, such as remifentanil, was used because of unacceptable respiratory depression. Remifentanil is more appropriately titrated to provide analgesia and comfort rather
than sedation.(11) In the present study, the OAA/S score of 4 was used as an indicator of sedation and the degree of sedation was easily titrated with the infusion rate of remifentanil.

The administration of sedative or analgesic agents during regional anesthesia necessitates close monitoring of respiratory function and provision of oxygen supplementation. However, oxygen supplementation and pulse oximeter monitoring may not prevent high levels of carbon dioxide. Therefore continuous clinical assessment of respiratory function or end-tidal carbon dioxide measurements should be applied when opioids are used for sedation as previously mentioned by Servain et al.(17)

In conclusion, remifentanil may be a useful adjunct for analgesia-based sedation and comfort at a dose of $3.07\pm0.79 \mu g/kg/hr$ without risk of significant hemodynamic instability during spinal anesthesia in elderly patients. Due to frequent occurrence of remifentanil-induced respiratory depression, this agent should be used cautiously, and we recommend continuous and careful monitoring of respiratory function during its use.

**ABSTRACT**

**Purpose:** Remifentanil may be a useful adjunct for spinal anesthesia because of its titratability and hemodynamic stability. The aim of this study was to determine the appropriate dosage and efficacy of remifentanil as an adjunct in elderly patients under spinal anesthesia.

**Methods:** Remifentanil 0.5 $\mu g/kg$ was administered 90 seconds before performing spinal anesthesia, followed by continuous infusion with 3 $\mu g/kg/hr$ in 43 elderly patients and the rate was titrated by steps of 0.5 $\mu g/kg/hr$ at 15-minute intervals as required to achieve an adequate sedation (Observer’s Assessment of Alertness/Sedation Scale 4). Safety was assessed by respiratory and hemodynamic monitoring.

**Results:** The mean infusion rate of remifentanil to maintain an adequate sedation without clinically significant adverse event was $3.07\pm0.79 \mu g/kg/hr$. Transient respiratory depression was developed in 29% of patients.

**Conclusions:** Remifentanil may be a useful adjunct for analgesia-based sedation at a dose of $3.07\pm0.79 \mu g/kg/hr$ in elderly patients under spinal anesthesia. However, frequent occurrence of remifentanil-induced respiratory depression requires careful monitoring and cautious administration.

**Key Words:** Anesthesia, Spinal, Remifentanil

**REFERENCES**