COMPARISON OF ANESTHETIC PROPERTIES OF KETOFOL (KETAMINE WITH PROPOFOL) AND PROPOFOL IN MINOR SURGICAL PROCEDURES

Karki SB¹*, Rajbanshi LK², Ariyal B², Khanal K¹

ARTICLE INFO
Article History
Received : 22 October, 2017
Accepted : 05 November, 2017
Published : 31 December, 2017

ABSTRACT
Introduction
Outpatient anesthesia for the minor day care surgical procedures requires a safe anesthesia and anesthetic agents. For this purpose two study solutions propofol with ketamine (ketofol) and propofol were compared. The comparison of the both agents were assessed, evaluated and discussed in this study.

Methodology
This is prospective study of 100 adult patients of both sex aged between 18-60 years with ASA physical status class I and II who were operated in the Birat Medical College teaching hospital. This study was started after approval from the ethical committee of the hospital and after written and informed consent from all participants.

All patients were randomly divided into two groups. Group A (n=50) received ketamine with propofol and Group B (n=50) propofol after intravenous sedation with 2 mg of midazolam and 1 mg of butorphanol. The main aim of this study was comparison of onset of sedation, respiratory and cardiac adverse events, level of sedation using Ramsey sedation scale, requirement of sedatives, recovery time, average cost of the sedatives and postoperative complications between the two groups. All collected data are analyzed using MS Excel office 2007 and for the data analysis IBM SPSS software was used.

Results
In the both groups patients were comfortable with the either anesthetic agents. Onset of anesthesia was faster in Group A. Intraoperative sedation was measured using Ramsay sedation scale and was comparable. Recovery from sedation was assessed with AVPU scale and patient was shifted to postoperative room after the verbal response. Postoperative complications seen were nausea vomiting, severe pain, ketamine induced psychotomimetic effects and all of these were treated well and discharged on the same day from the hospital.

Conclusion
The combination of ketamine and propofol for the sedation in minor surgical procedures has more advantages than the propofol alone. The combination is cost effective, has better sedation and hemodynamic stability, quick recovery and fewer side effects in the post operative room.

KEYWORDS
Anesthesia; ketofol; propofol; surgery

* Corresponding Author
Dr. Shambhu Bahadur Karki
Consultant Anaesthesiologist
Department of Anaesthesia and Intensive Care
Birat Medical College & Teaching Hospital
Email: karkisb@yahoo.com
INTRODUCTION

Minor surgical procedures are outpatient daycare procedures in which patients are admitted, surgical interventions are performed and discharged at the same day. Such outpatient anesthesia demands a safe anesthesia method with the short acting intravenous anesthetic medications, which are able to provide rapid anesthesia depth and hemodynamic stability, rapid metabolism and minimum adverse effects in the recovery period.¹²⁻³

Propofol is a short acting anesthetic agent which is used widely for the induction of anesthesia and for the sedation in minor surgical procedures. It is a non opioid, non barbiturate sedo-hypnotic agent with rapid onset and short duration of action.¹ It produces good sedation and also has antiemetic effect.² Its adverse effects are dose related respiratory and cardiovascular depression, bradycardia and pain during injection.³⁴ Propofol is known to produce amnesia with sedative and hypnotic effects but it don't have analgesic property so combination of analgesic molecule is required with propofol for the sedation in surgical procedures.³

Ketamine is a phencyclidine derivative which blocks the NMDA receptors and provides dissociative anesthesia, profound analgesia and amnesia.³ Ketamine increases heart rate, cardiac output and blood pressure and it has little or no cardiovascular and respiratory depression. It's wide spread use as a sole anesthetic agent for procedural sedation in adults is limited because of its psychotomimetic effects such as vomiting and laryngospasm. The incidence of emergence hallucination effects can be reduced by coadministration of benzodiazepine, barbiturates or propofol.³ Ketamine has similar effects as propofol at sedative and hypnotic levels but it don’t have analgesic property so combination of analgesic molecule is required with propofol for the sedation in surgical procedures.³

Ketamine and propofol has been used in separate syringes in the same patient successfully in variety of procedures including sedation of spinal anesthesia, minor ophthalmological procedures, gynecological and surgical procedures in children and adults.³ The main advantage of this combination is the opposing effect in the hemodynamic and respiratory effects of each drug.⁴⁻⁶ In a prospective study carried by Friedberg et al in 1264 patients undergoing anesthesia for the surgical procedures with Ketofol (ketamine with propofol), concluded that this combination is safe and effective.³ The combination of ketamine with propofol has been shown to reduce the dose of either molecule required for the sedation and analgesia. The reduced doses of this combination provides safe, cost effective and less toxic anesthetic agent than the either drug alone.³

The main objective of this study is to compare sedo-analgesia effects of both anesthetic drugs using Ramsay Sedation Score, intraoperative complications with hemodynamic and respiratory changes, requirement of amount of anesthetic solutions, recovery times, cost of the either solutions and postoperative complications in minor surgical procedures.

METHODOLOGY

This is a prospective study conducted in the Birat Medical College teaching hospital, Biratnagar, Nepal after obtaining approval from the ethical committee of the hospital and after written informed consent from all participants from February 2017 to April 2017. Total 100 patients between 18-60 years old with the ASA physical status class I and II were included in the study.

Inclusion criteria:
1. Age between 18-60 years
2. Patients with ASA physical status class I and II
3. Minor surgical procedures lasting for less than 30 min

Exclusion Criteria:
1. Pregnant women
2. Patients with ASA physical status class III and IV
3. Surgical procedures lasting more than 30 min
4. Patients who refused to give consent for the study
5. Patients with ASA physical status class III and IV
6. Paents who refused to give consent for the study

A routine preoperative fasting of 8 hours was mandatory for all patients. Patients were taken to operating room after pre anesthesia evaluation and preparation. Intravenous line was opened in operating room with 2G intravenous cannula and RL solution was regularly infused. 4 L/min of oxygen was delivered to all patients via face mask during surgery and recovery period. Parameters monitored in the operating room were ECG, NIBP, pulse oxymetry, respiration and sedation score were recorded as follows:
- before induction
- after incision
- Every 5 min during surgery
- at the end of the procedure

Table 1. RAMSAY SEDATION SCALE.⁶

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. AWAKE</td>
<td>Patient anxious, agitated or restless or both</td>
</tr>
<tr>
<td>2. Patient cooperative, oriented and tranquil</td>
<td></td>
</tr>
<tr>
<td>3. Patient respond to commands</td>
<td></td>
</tr>
<tr>
<td>4. ASLEEP</td>
<td>A brisk response to a light glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>5. A sluggish response to light glabellar tap or loud auditory stimulus</td>
<td></td>
</tr>
<tr>
<td>6. ASLEEP</td>
<td>A brisk response to a light glabellar tap or loud auditory stimulus</td>
</tr>
</tbody>
</table>

All patients were induced with 1 mg of inj butorphanol and 2 mg of Inj midazolam intravenously. The study solution of Group A was prepared with 50 mg (1 ml) of Ketamine, 50 mg (5 ml) of Propofol and 4 ml of Normal Saline (NS) in a 10 ml syringe. The ratio of 1:1 was designed for ketofol group.

Group A patients received 50 mg (5 ml) Ketofol (25 mg
Hemodynamic parameters (pulse rate, NIBP) increased at the me of incision but were within the acceptable level. Respiraon rate was decreased and was shallow in many paents. SpO2 was decreased below 90% in 32 cases and apnea was seen in 12 cases, all treated with posive pressure venlaon with oxygen. Respiratory depression was seen more frequently in the Propofol group than in the Ketofol. In this study 19 paents had shallow and slow respiraon and 5 paents had apnea in Propofol group where as 13 paents had shallow and slow respiraon and 7 had apnea in Ketofol group. There was no significant change in vital parameters aer 5 min and at the end of the surgery. There was no decrease in SBP and pulse rate seen in any cases.

The intermittent top ups was administered to the either group according to the autonomic (pulling extremies, eye opening, crying) and hemodynamic (tachycardia, hypertension) responses. The sedaon level was assessed with the help of Ramsey Sedation Scale (RSS) and was maintained between 4-5 score. All vital parameters were recorded before induction of anesthesia, just after incision and every 5 min during the procedure. The induction time, surgical and recovery times were recorded and analyzed using mean with SD and listed in Table 5. Patients were transferred to postoperative room when they were able to open their eye, protrude the tongue and obey the verbal command according to the AVPU recovery scale. All parameters were closely monitored in postoperative room along with any adverse events and requirement of additional drugs. Inj diclofenac sodium 75 mg IM prescribed for the management of postoperative pain and Inj metoclopramide 10 mg IV for the postoperative nausea vomiting (PONV).

All recorded intraoperative and post operative data were collected and analyzed using SPSS. Results are expressed as mean ± SD percentage and frequency.

RESULTS

The study was conducted during 3 months period in which 50 patients had procedural sedaon with ketofol (propofol and ketamine) and 50 patients with propofol. Patient demographics are listed in table 3. The demographic data of the both groups were similar and comparable. No statistical differences seen between the groups for patient’s age, sex, weight and ASA classificaon. The level of sedaon was assessed using Ramsey Sedation Scale (RSS) and in the both groups RSS, operating time and recovery time were comparable (P>0.05).

Table 3. Demographic data.

<table>
<thead>
<tr>
<th></th>
<th>Group A ( No:50)</th>
<th>Group B ( No: 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years) mean±SD</td>
<td>33.27± 1.32</td>
<td>30.38±1.28</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>33:17</td>
<td>35:15</td>
</tr>
<tr>
<td>ASA I:II</td>
<td>39:11</td>
<td>41:9</td>
</tr>
<tr>
<td>Weight(kg) mean±SD</td>
<td>57.9 ±8.7</td>
<td>60.8 ±6.5</td>
</tr>
<tr>
<td>Duration of Surgery</td>
<td>16.19 ± 7.5</td>
<td>17.26 ± 5.4</td>
</tr>
</tbody>
</table>

The mean induction time required for the Ketofol group was 32.18±4.17 sec and for propofol group it was 39.34±5.12sec. Similarly the mean surgical and recovery time also comparable in both groups. The minimum requirement of anesthec solution in Ketofol group was 5 ml and in Propofol group it was 8 ml. The average requirement of sedaon was 9.16±4.32 ml in Ketofol group and was 13.42±3.24 ml in Propofol group. The requirement of the anesthec solution in ketofol group was much less than the propofol group and is statistically significant (P˂0.05). The average surgical time was 16.19±7.5 min in Ketofol group and was 17.26±5.4 min in Propofol group and was statistically comparable (P>0.05).

No intra operative nausea and voming seen in any case of both groups. The AVPU scale was used to assess the recovery status of all patients and all transferred to the post operative room only after the verbal response. The average recovery time was 4.26±2.19 min in Ketofol group and 5.16±3.48 min in Propofol group.
All postoperative patients were kept at least for 4 hours in postoperative room and then discharged if there were no any adverse events. Post operative pain was assessed with Verbal Rating Scale (VRS) using 0 for no pain, 1 for slight pain, 2 for moderate and 3 for the severe pain and 4 for the severe unbearable pain (Table 2).

<table>
<thead>
<tr>
<th>Table 5. Comparison of anesthesia parameters.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
</tr>
<tr>
<td>Mean induction time (sec)</td>
</tr>
<tr>
<td>Mean surgical time (min)</td>
</tr>
<tr>
<td>Mean recovery time (min)</td>
</tr>
<tr>
<td>Study solution (ml)</td>
</tr>
<tr>
<td>Ramsay sedation scale</td>
</tr>
</tbody>
</table>

Intramuscular analgesic solution diclofenac sodium was prescribed when VRS was 3 or more. Out of 100 analyzed patients 23 patients demanded analgesia, 9 from the ketofol group and 14 from propofol group due to severe pain (VRS 3, 4) and were treated with IM injection of 75 mg of diclofenac sodium. Rest of the patients had minimal pain or bearable pain.

Table 6. Postoperative Complications.

<table>
<thead>
<tr>
<th>Table 6. Postoperative Complications.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (Ketofol)</td>
</tr>
<tr>
<td>Postoperative pain (No)</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Psychotomimetic effects</td>
</tr>
</tbody>
</table>

Postoperative nausea vomiting seen in 8 patients where 5 patients developed nausea in ketofol group and 2 in propofol, however vomiting seen only in 1 patient of ketofol group and 14 from propofol group due to severe pain (VRS 3, 4) and were treated with IM injection of 75 mg of diclofenac sodium. Rest of the patients had minimal pain or bearable pain.

The combination of propofol and ketamine produces more stable hemodynamic condition than ketamine or propofol used individually. Ketamine with propofol for the sedation is gaining popularity due to the increased analgesic effect of ketamine and reduction of the side effects of propofol. Ketamine is a non barbiturate dissociative anesthetic agent acts primarily as an antagonist of the NMDA receptors. According to WHO 2 mg per kg of ketamine given intravenously over 60 seconds produces surgical anesthesia within 30 seconds which continues for 5-10 min and resolves completely in 1-2 hours. Analogic effect of ketamine can be obtained by intravenous administration of 0.2-0.75 mg/kg (WHO). Ketamine is a mild respiratory depressant and also has a bronchodilatory effect with maintained pharyngeal and laryngeal reflexes. Ketamine is only available intravenous anesthetic agent having an analgesic, sedo-hypnotic and amnestic properties and least economical than any other similar agents. So ketamine can be successfully used as an ideal anesthetic agent producing analgesia, unconsciousness, amnesia and akinesia. Being all the benefits, ketamine is four times cheaper than the propofol so its cost effectiveness is also responsive for its increased use in operating room, emergency and intensive care department and field surgery.

Ketamine is a strong analgesic which effectively reduces the injection pain of propofol by attenuating the afferent pain pathways. Ketofol is mixture of ketamine and propofol in a same syringe in various concentration used effectively as an inducing agent in operating room and in ambulatory setting. It is also believed that these two agents have synergistic effect for the sedation and at the same time counteract the side effect of each other. In a study by Khajabi et al the ketofol has shown to have an effective sedative property and is better than other combination of propofol with fentanyl and pethidine. In addition, the ketofol combination has low incidence of psychomimetic reaction of ketamine seen in the postoperative room. These two molecules can be successfully mixed in a single syringe in 1:1 proportion without any chemical changes.
which was investigated by several authors and found that such proportions is safe and efficient for analgesia and sedation. It is also reported that ketamine and propofol are physically compatible and chemically stable and can be mixed in a single syringe and the mixture can be stored too. 

Triss LA investigated about the compatibility of propofol with other various agents and reported that ketamine and propofol are physically compatible for 1 hr at 23⁰ C. In another study done by RF Donnelly the combination of ketamine and propofol in either 50:50 or 30:70 proportion in a plastic syringe were physically and chemically stable for at least 3 hr when stored at room temperature with exposure of light. In this study ketofol mixture was prepared freshly just before the induction and the remaining drug stored in refrigerator and used within 3 hr. Ketamine also has antibacterial and antifungal activity against some organisms in propofol, which is known to be a growth promoting solution for microorganisms. So the combination of both solutions in a single syringe may reduce the risk of infection caused by accidental contamination of the mixture.

Badrinath et al used different concentration of ketamine–propofol combination for sedation for female patients undergoing breast biopsy and did not encounter any severe respiratory complications. In this study minor respiratory complications seen in the both groups and were transient apnea and decrease in SpO2 below 90% and all treated with positive pressure ventilation with O2. The minimum dose of study solution required in Ketofol group was 5 ml and in Propofol group it was 8 ml and the average requirement of Ketofol was 9.16±4.32 ml and in Propofol group 13.42±3.24 ml. This study was also carried out to find the cost effectiveness of the mixture of ketamine and propofol too. The average requirement of study solution in Group A was 9.16 ml means 45.8 mg of propofol and 45.8 mg of ketamine. The price of 10 mg of propofol is 16 rupees and 10 mg of ketamine is 4 rupees, so the price of 9.16 ml of study solution of group A is 91.6 rupees, however in the propofol group the cost of the 13.42 ml (134.2mg) of the solution is 214.72 rupees. In this study ketofol group provided similar anesthesia for minor surgical procedures with more than two times cheaper than the propofol group and is statistically significant (P<0.05).

All patients were comfortable in the postoperative room and discharged after four hours of surgery and no any patient was admitted due to the postoperative complications. The only seen postoperative complications were pain, hallucinations, nausea and vomiting and all treated successfully and discharged at the same day.

CONCLUSION

The combination of ketamine and propofol has several advantages over the propofol alone for the anesthesia in minor surgical procedures. The combination is cost effective, better sedation and analgesia, hemodynamic stability and quick recovery seen in the operating room. The combination has less adverse effects than the either drug alone due to their complementary effects of lowering the dose of both drugs.

CONFLICT OF INTEREST

None.