Comparative evaluation of propofol-ketamine and propofol-fentanyl for minor surgical procedures

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ABSTRACT

Background: Aim of the present study was to compare the clinical efficacy of combination of propofol-ketamine and propofol-fentanyl in terms of haemodynamic variables, recovery profile and side effects.

Methods: The study enrolling 120 patients of (age 20-50 years) ASA grade I & II were randomly allocated in two groups of sixty each. They were undergoing short surgical procedures lasting up to 20 minutes. Group I received injection ketamine 0.5 mg/kg over 2 minutes followed by injection propofol at rate of 1 ml over 3 seconds till the end point of induction (till loss of consciousness and loss of eye lash reflex). Group II received injection fentanyl 1.5 µg/kg followed by 1 ml propofol till the end point of induction and maintenance of anesthesia. Hemodynamic variables were recorded pre, intra and postoperatively at regular intervals. Recovery and side effects was also assessed. The results were tabulated and analyzed statistically.

Results: Patients in both the groups produce minor haemodynamic changes and did not differ significantly. The recovery time was longer in group I as compare to group II. We found no complications of serious type except vomiting and nausea in group II. Discharge criteria were significantly earlier in group I than group II.

Conclusions: Both propofol-ketamine and propofol-fentanyl was useful for short surgical procedures but propofol-ketamine group offers more advantage.

Keywords: Propofol, Ketamine, Fentanyl, Hemodynamic variables, Recovery time

INTRODUCTION

The rapid recovery to “home readiness” with a minimum side effect is an important goal in ambulatory anaesthesia. The concept of ambulatory anaesthesia is emerging as a need of time for day case surgery. The anaesthesia technique for such surgeries should be simple, economical and easy to practice. The ambulatory surgeries are beneficial because of minimal postoperative morbidity and mortality, clear headed recovery and “street fitness”, cost-effectiveness and convenience to the patients and surgeons.

Number of studies have shown propofol to have favourable recovery characteristics especially for short surgical anaesthesia and often considered to be drug of choice for short ambulatory procedures. Although there is no gold standard for short outpatient anaesthesia, propofol has been claimed by many anaesthesitist to be the best induction agent, because of its clear headed nature of the recovery and low incidence of postoperative nausea and vomiting. Various studies reported that propofol can be used satisfactorily as a sole anaesthetic agent for day care surgery when analgesics are used as an adjuvant along with it. The choice of premedication as well of adjuvant to propofol is always a matter of differing opinion, some advice opioid premedication, some offers benzodiazepines. Similarly various adjuvants like ketamine, fentanyl, alfentanil or other opioid analgesic have been used as adjuvant.
Ketamine is a potent analgesic, its anaesthetic and analgesic effects have been suggested to be mediated by different mechanisms. Ketamine in subanaesthetic doses with propofol has gained attention in total intravenous anaesthesia because of its powerful analgesic action in a small dose without causing myocardial and respiratory depression. Ketamine also causes some degree of sympathetic stimulation, which tends to counter balance the cardiovascular effects of propofol. It has very high margin of safety, no irritation of the veins and no negative influence on ventilation or circulation except the disadvantage of producing hypertension and psycho mimetic emergence phenomena.

Fentanyl on the other hand is the most frequently used opioid in clinical anaesthesia today. Fentanyl is synthetic opioid analgesic, which has rapid onset and short duration of action and has been used in combination with propofol for total intravenous anaesthesia satisfactorily.

Acknowledging the view of the various authors, ketamine and fentanyl was compared as pre induction adjuvants to propofol for short surgical procedures like closed reduction fracture upper limb, incision and drainage of abscesses, dilatation and curettage and dilatation and evacuation. The study was design to assess the intraoperative, postoperative stability of the haemodynamics, respiratory parameters as well the recovery profile in both the propofol-ketamine and propofol-fentanyl groups. Overall recovery and the benefits were assessed by discharge criteria and which group offers more advantage was evaluated.

METHODS

The present study was carried out in the Department of Anaesthesiology at Government Medical College and Hospital, Nagpur, Maharashtra. After obtaining institutional ethical committee approval and patients written informed consent, the study was conducted in 120 patients, aged 20–50 years of ASA grade I or II, scheduled for short surgical procedures i.e. incision and drainage of abscesses, closed reduction of fracture upper limb, dilatation and curettage and dilatation and evacuation lasting up to 20 minutes. The patients were randomly allocated to the two treatment groups (60 of each) with a block size 10 and allocation ratio 1:1. Patients with systemic and metabolic diseases such as cardiovascular, respiratory, neurological and liver diseases, patients who received any analgesic or narcotic in the preceding 48 hours, patients of ASA grade III and IV were excluded from study. A detailed pre-anaesthetic evaluation including history and a thorough general and systemic examination and all relevant investigations were done for all the patients.

All patients were kept fasting for at least 6 hours prior to anaesthesia. Preoperative baseline heart rate, blood pressure, respiratory rate, SpO2 was recorded. A peripheral intravenous line was established. All patients were premeditated with ranitidine 50 mg + glycopyrrolate 0.2 mg + midazolam 1 mg 5 min prior to induction. Group I received injection ketamine 0.5 mg/kg over 2 minutes followed by injection propofol at rate of 1 ml over 3 seconds till the end point of induction (till loss of consciousness and loss of eye lash reflex). Group II received injection fentanyl 1.5 µg/kg followed by 1 ml propofol till the end point of induction.

Intraoperative, heart rate, blood pressure, respiratory rate and oxygen saturation were recorded at different time intervals of 1, 3, 5, 10, 15 and 20 minutes following induction of anesthesia in both the groups. Throughout procedure patients were allowed to breathe atmospheric air and oxygen supplementation 4 lt/minutes via mask was given to some patients during apnoea. Top up dose of propofol (25 mg) was given when the patient became light during anesthesia as indicated by rise in heart rate, blood pressure, lacrimation or any movement to surgical stimuli. Total dose of propofol required for the patients was noted. Recovery from anesthesia at the end of surgery was assessed by loss of eyelash reflex to spontaneous eye opening as well as responding to verbal commands i.e. orientation of time, place and person.

Postoperatively, all vital parameters were recorded every 10 minutes. Any complication e.g. nausea, vomiting, delirium, giddiness, sedation, pain, headache, diplopia were noted till 1 hour in the recovery room. After 1 hour patients were shifted to ward. The patients were discharged from the ward according to routine criteria for day care surgery (Conscious oriented, able to drink and void, walk without assistance, without postoperative nausea and vomiting, pain free, haemodynamically stable) and discharge time was recorded. At the time of discharge, Coin test for recovery was performed, in which after discontinuation of anesthesia the time when patients were able to count the number of coin and sum up their values correctly was noted.

Discharge criteria of the patients evaluated by Modified post anesthesia discharge scoring system (Ronald D Millar).

A. Vital signs
   2 - Within 20% of basal
   1 - 20–40% of basal.
   0 - 40% of basal
B. Ambulation
   2 - No dizziness.
   1 - With Assistance
   0 - Dizziness
C. Nausea and vomiting
   2 - Minimal
   1 - Moderate
   0 - Severe
D. Pain
   2 - Minimal
   1 - Moderate
   0 - Severe
E. Surgical bleeding
   2 - Minimal
   1 - Moderate
   0 – Severe

Total points were allotted to each parameter e.g. vital sign, ambulation, nausea and vomiting, pain, surgical bleeding etc and total score was calculated. With patients scoring 9 or more was considered to be fit for discharge.

**Statistical Analysis**

Continuous variables (age, weight, height, pulse rate, systolic blood pressure, diastolic blood pressure, respiratory rate, SpO₂, induction time, total dose of propofol, recovery profile, discharge time and discharge score etc) were presented as mean ±SD. Continuous variables were compared at different time intervals between ketamine and fentanyl groups by performing unpaired t-test p <0.05 were considered as statistical significant. Dada was analysed a statistical software STATA VERSION 8.0.

**RESULTS**

A total of 120 patients who underwent short surgical procedures lasting up to 20 minutes were enrolled for the study and were randomly divided into two groups. The demographic profiles of the patients in both the groups were comparable with regards to age, weight and height, (Table 1). The distribution as per ASA status was similar in both the groups and patients were allocated to both groups in equal ratio, male:female (1:1).

**Table 1: Comparison of demographic data of the patients.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group – I (n = 60)</th>
<th>Group -II (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ( yrs)</td>
<td>30.3±6.78</td>
<td>33.75±8.44</td>
</tr>
<tr>
<td>Weight (kgs)</td>
<td>52.65±7.38</td>
<td>53.05±7.13</td>
</tr>
<tr>
<td>Height ( in cms)</td>
<td>160.26±5.83</td>
<td>159.13±6.54</td>
</tr>
</tbody>
</table>

Above data indicates that the study groups i.e. group I and groups II was statistically comparable with regard to age, weight and height of the patients.

Pre-induction pulse rate, systolic blood pressure, diastolic blood pressure, respiratory rate and arterial saturation were comparable in both the groups with a statistically no significant difference between them (p>0.05). Intraoperatively, the pulse rate was slightly increased in group I with the maximum rise at 5 minutes which was statistically significant (p<0.001) compared to preinduction value (91.33±7.73 to 98.13±6.64/min). Contrary to group I, group II patients showed minimal decrease in pulse rate post induction and during maintenance from basal 87.13±8 to 84.35±8.09/min, (p<0.001). The difference in pulse rate in both the groups was statistically significant (p<0.001) (Table 2).

In group I, we found no statistically significant change in intraoperative mean systolic blood pressure, when basal line mean value of 115.63±6.43 mmHg was compared to 3 minutes (115.4±7.31 mmHg) and at 5 minutes (116.7±7.38 mmHg). Mean value of systolic blood pressure at 10, 15 and 20 minutes minimal change was observed showed haemodynamic stability. Whereas in group II minimal deceased in systolic blood pressure was noted after induction from basal reading of 110.26±5.40 mmHg, showing comparably stable haemodynamics, (Table 3). The mean diastolic blood pressure remained unchanged throughout intraoperative period as compared to base line value in both the groups. In group I DBP was 78±6.82 to 77.86±5.53 mmHg and in group II was 77.8±4.96 to 78.3±5.85 mmHg. Whatever minimal changes in mean diastolic blood pressure at different time intervals they were statistically insignificant in both the groups (p>0.05) (Table 4).

There was minimal change in respiratory rate during post induction and maintenance at different time interval in group I (20.01±2.81/min to 21.06±1.99/min) and even up to 20 minutes. In group II the respiratory rate decreased from the pre induction value and the decrease was statistically significant till 20 minutes post induction (19.9±2.63/min to 16.7±1.46/min) (Table 5). The mean arterial oxygen saturation in the perioperative period in group I was found to be in the range of 98.1±0.96% to 99.41±0.90% whereas in group II SpO₂ was 97.21±1.50 to 98.18±1.44%. The changes in mean arterial oxygen saturation at different time interval were statistically insignificant (p>0.05) (Table 5).

Recovery time in either groups P-K and group P-F as judged by spontaneous eye opening and orientation to time, place and person was longer (12.61±2.83 and 20.60±4.20/min) in group I (P-K) as compared to group II (P-F) (10.42±1.90 and 18.73±2.62/min). P value <0.001 showed significant difference in delayed recovery in group I (P-K) (Figure 1).
### Table 2: Comparison of pulse rate at different time intervals in both the groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Pre-induction (basal)</th>
<th>Mean pulse rate at different time intervals (min) post induction and during maintenance of anaesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 min</td>
</tr>
<tr>
<td>Group I</td>
<td>91.33±7.73</td>
<td>95.23±8.78</td>
</tr>
<tr>
<td>Group II</td>
<td>87.13±8.00</td>
<td>83.5±8.31</td>
</tr>
<tr>
<td>P value</td>
<td>-</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Data are Mean and ±SD, < 0.001 - Statistically significant (S).

### Table 3: Comparison of systolic blood pressure at different time intervals in both the groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Pre-induction (basal)</th>
<th>Mean systolic blood pressure at different time intervals (min) post induction and during maintenance of anaesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 min</td>
</tr>
<tr>
<td>Group I</td>
<td>115.63±6.43</td>
<td>113.8±9.01</td>
</tr>
<tr>
<td>Group II</td>
<td>110.26±5.40</td>
<td>107.36±5.49</td>
</tr>
<tr>
<td>P value</td>
<td>-</td>
<td>&gt; 0.3906</td>
</tr>
</tbody>
</table>

Data are Mean and ±SD, > 0.05 - Statistically insignificant (NS).

### Table 4: Comparison of diastolic blood pressure at different time intervals in both the groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Pre-induction (basal)</th>
<th>Mean diastolic blood pressure at different time intervals (min) post induction and during maintenance of anaesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 min</td>
</tr>
<tr>
<td>Group I</td>
<td>78±6.82</td>
<td>79.56±6.79</td>
</tr>
<tr>
<td>Group II</td>
<td>77.8±4.96</td>
<td>78.26±5.69</td>
</tr>
<tr>
<td>P value</td>
<td>-</td>
<td>&gt; 0.0566</td>
</tr>
</tbody>
</table>

Data are Mean and ±SD, > 0.05 - Statistically insignificant (NS).

### Table 5: Comparison of respiratory rate and SpO2 at different time intervals in both the groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Pre-induction (basal)</th>
<th>Mean respiratory rate at different time intervals (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 min</td>
</tr>
<tr>
<td>Group I</td>
<td>20.01±2.81</td>
<td>18.9±1.72</td>
</tr>
<tr>
<td>Group II</td>
<td>19.9±2.63</td>
<td>16.65±1.17</td>
</tr>
<tr>
<td>P value</td>
<td>-</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Groups</th>
<th>Pre-induction (basal)</th>
<th>Mean arterial oxygen saturation at different time intervals (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 min</td>
</tr>
<tr>
<td>Group I</td>
<td>98.91±1.06</td>
<td>98.1±0.96</td>
</tr>
<tr>
<td>Group II</td>
<td>98±1.14</td>
<td>97.21±1.50</td>
</tr>
<tr>
<td>P value</td>
<td>-</td>
<td>&gt; 0.9101</td>
</tr>
</tbody>
</table>

Data are Mean and ±SD, < 0.001 - Statistically significant (S) and > 0.05 - Statistically insignificant (NS).
Side effects and complications were minimal in both groups except the pain on injection was observed in 8 (13.3%) patients in group II, whereas no pain on injection was observed in group I receiving ketamine. Apnoea was observed for 20 seconds in 8 (13.3%) patients of group II whereas in 2 (3.3%) patients in group I, which was treated with oxygen mask and intermittent positive pressure ventilation. In group II, 9 (15%) patients had PONV, 6 (10%) patients complained pain at the site of injection and 2 (3.3%) patients had giddiness in recovery room. These side effects were minimal in group I. There was no incidence of hypoventilation, laryngeal spasm, involuntary movement, episode of the desaturation (SpO₂ <90) in either of the groups.

The discharge times in both the groups were comparable. It was more in group II (104±10.87 min) as compared to group I (93.33±7.42 min). At the time of discharge, the mean discharge score was calculated in group I and in group II was 9.68±0.47 and 9.58±0.49 respectively.

**DISCUSSION**

An anaesthetic technique using a minimum number of agents is sought with the increase in day care surgery; which provides the essential element of balanced anaesthesia combined with rapid return of street fitness. The rapid recovery to home readiness with a minimum side effect is an important goal in ambulatory anaesthesia. The ideal profile for a single anaesthetic agent includes a rapid onset of anaesthesia, short duration of action, lack of cumulation on repeated administration, an absence of excitatory effects during induction and recovery and minimal postoperative sequelae.

Propofol, since its introduction in 1986 has been shown to have many of these properties; previous studies have been performed to assess propofol both as a sole anaesthetic agent and in combination with fentanyl. Few authors have studied its combination with ketamine also. However there very few direct comparisons with these combinations for day case anaesthesia. Whether pre induction with ketamine or fentanyl in combination with propofol for short surgical procedures offered any better advantage considering the better quality of anaesthesia, minimal side effects and good recovery profile was studied and compare to know the advantage of one combination over the other in the intraoperative and postoperative period.

In the present study, group I (P-K) received ketamine 0.5 mg/kg as well as group II (P-F) received fentanyl 1.5 μg/kg two minutes before induction. Similar dose regimen was used by Saha K et al.8 After giving ketamine and fentanyl, propofol was given in concentration of 1% at the rate of 1 ml/3 sec till loss of eye lash reflex. The rate of injection of propofol was kept constant at approximately 1 ml/sec according to Rolly G et al.9 The total dose of propofol required in group I was 120.75±18.56 mg and in group II 137.75±19.53 mg. The dose of propofol for induction and maintenance of anaesthesia was less in group I. This could be because when propofol and ketamine were used in combination was seen to be hypnotic at anaesthetic end points. Moffat AC et al7 showed that total dose of propofol to be 129±83.8 mg almost similar to present study.

We found statistically significant changes in pulse rate in both the group’s up to 10 minutes but no episodes of bradycardia or tachycardia. This finding was comparable with those of Saha K et al.8 Although the increase in pulse rate in group I may be due to the sympathetic stimulation by ketamine and the decrease in pulse rate in group II can be attributed to action of fentanyl on CVS, these result compared with study of Mayer M et al,10 Hui TW et al,11 Tan CH et al,12 Saha K et al.8 When comparing intraoperative systolic blood pressure in both the groups, it was noted that majority of the patients had stable hemodynamic throughout the procedures. The minimal rise in post induction systolic blood pressure was observed after 5 minutes in group I receiving ketamine. In group II, maximum patients had systolic blood pressure in the range of 100 to 110 mmHg at various time intervals, showing cardio stable action of fentanyl as compared to ketamine. The changes in the mean systolic blood pressures in both the groups at 3 and 5 minutes intervals after induction were statistically significant (p<0.0027 and p<0.045 respectively). Our findings were similar to the study done by Tan CH et al,12 Saha K et al.8 The mean diastolic blood pressure remained unchanged throughout intraoperative period compared to base line in the both groups with minimal clinical fluctuations. These minimal changes in both the groups at different time interval were statistically insignificant. The mean diastolic pressure was not measured by any authors in their study. Thus we found comparatively stable hemodynamics in both the groups. The opposing effect of ketamine and propofol on arterial pressure tended to cancel each other out resulting in improved cardiovascular stability. No incidence of hypotension was reported in the present study.

In group I, 33 patients had basal respiratory rate of 19 to 25/min, but after induction up to 15 minutes number of patients in this range increased to 42 (70%) and 44 (73.3%) patients at 5 and 10 min respectively. Ten patients showed higher respiratory rate (more than 25) at 10 min in group I whereas majority of the patients in group II exhibited the respiratory rate in the range of 12 to 18/min throughout the surgery. No patient had respiratory rate >25 in this group showing action of fentanyl. There were very minimal changes in mean respiratory rate in post induction and maintenance at different time intervals up to 10 min in group I and even at 15 and 20 min while in group II minimal decrease in mean respiratory rate was found up to 20 minutes. The minimal decreases in respiratory rate in group II may be due the respiratory depressant action of fentanyl and propofol. Saha K et al7 found that the respiratory rate was significantly low in group II (P-F) at 1 min, 3 min and 5
We found prolong recovery time in ketamine group as compared to fentanyl group, prolongation could be because of maximum peak effect of ketamine (5 to 10 min). The time required for the patients to have orientation of time, place and person from time of onset of induction was noted by asking the patient his name and recognition of the known object and some question about environment for e.g. where are you? Where is your house, etc? Although the mean time required for orientation of time, place and person from time of onset of induction was longer in group I than group II. The P value <0.036 showed significant difference in both the group. Less than 4% of ketamine was excreted unchanged in urine and 16% patients appears as hydroxilated delivative, so large fraction of ketamine remained in unchanged form resulting in cumulative effect leading to delayed recovery. Therefore patient in propofol-ketamine group might have delayed recovery. This is in agreement with study done by Saha et al8 and Hernandez C et al.13

During procedure, patients were observed for any complication e.g. pain on injection, episode of hypoventilation (RR<8/min), laryngeal spasm, apnoea, involuntary movement, episode of desaturation (SpO₂<90%). Ten percent patients in group II had pain at injection site compare to none in group I. This could be attributed to local anaesthetic action shown by ketamine on intravenous injection. Eight patients in group II had transient apnoea (<20 sec) versus two patients in group I. This might be due to respiratory depressant action of fentanyl. Episodes of PONV were higher in group II because of fentanyl’s central emetic action. Other complications in the intraoperative period were minimal and statistically comparable. These findings concordance with study of Jakobsson J et al., Jakobsson J et al., Hui TW et al., Tan CH et al., Saha K et al., Akin A et al.

In the present study, majority of patients were discharged at 91 to 93 min in group I and at 96 to 100 min in group II. In group II patients required prolonged time of discharge could be due to longer duration of action of fentanyl. Both groups were quite comparable in achieving the ideal score of discharge. The discharged times in both the groups were comparable and statistically significant (p<0.001). The result of present study as per the discharge time was similar with study done by Jakobsson J, Saha K, Akin A et al.

CONCLUSIONS

Both propofol-ketamine and propofol-fentanyl combinations were comparable to each other in terms of haemodynamic parameters and recovery profiles, till end of surgery and in postoperative period. The recovery was delayed in group I. There were no complications of serious type except vomiting and nausea in group II. Overall discharge time was almost comparable.

Thus it can be concluded that both combinations were useful for short surgical procedures, but still ketamine has an upper edge.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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