Bispectral index (BIS) guided comparison of ketamine-propofol or fentanyl-propofol combinations when used in day care urological surgeries

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Abstract

Introduction and Aims: With the increased emphasis on early discharge after surgery, rapid recovery and early ambulation and cost effectiveness, use of short acting drugs like propofol, ketamine and fentanyl along with Bispectral Index (BIS) which allows titration of hypnotic drugs doses and may promote earlier awakening, we conducted this study to explore effectiveness of combinations ketamine-propofol and fentanyl-propofol in day care urological surgery guided by BIS.

Materials and Methods: After ethical approval and informed consent 140 patients scheduled for minor urological procedures on day care basis were randomised into two equal groups receiving ketamine-propofol and fentanyl-propofol combinations, to primarily observe haemodynamics, respiratory parameters, optimum sedation guided by BIS and recovery time in terms of Modified Aldrete Score (MAS) and secondarily total propofol consumption and side effects.

Results: Patients remained haemodynamically stable in group ketamine-propofol after induction while in group fentanyl-propofol there was significant fall in heart rate up to nine minutes after induction and blood pressure remained significantly low up to fifteen minutes. There was significant fall in respiratory rate and oxygen saturation but significantly early recovery with fentanyl with no significant difference in the incidence of side effects of apnoea, hypotension, bradycardia and nausea-vomiting and hallucination between the groups.

Conclusion: Ketamine-propofol combination produces rapid anaesthesia with stable haemodynamics while fentanyl-propofol combination allows faster awakening and reduces the length of stay in the post-anaesthesia recovery room. BIS monitoring optimize intraoperative condition and leads to significantly early recovery for faster home readiness in the ambulatory surgery.

Keywords: Day care surgery, Bispectral index, Modified aldrete score, Propofol, Ketamine, Fentanyl.

Introduction

Day care surgical procedures are those elective minor or intermediate surgeries performed under local, regional or general anaesthesia, on selected patients admitted and discharged on the same day of surgery with benefits of greater flexibility in scheduling, lower infection rates, respiratory and cardiovascular complication, early recovery and early ambulation and reduced over all procedural costs. Recent advances in anaesthetic and surgical techniques, combined with cost containment concerns, have made day-care surgeries increasingly popular.[1] Day care anaesthesia has dual goals of rapidly and safely establishing satisfactory procedural condition and ensuring rapid, predictable recovery with minimal postoperative sequels. With the introduction of modern shorter acting anaesthetics and sophisticated monitors like bispectral array (BIS) and electroencephalogram (EEG) monitors, ensuring fine titration of anaesthetic agents, it is possible that many patients will be able to go directly to the step-down unit, bypassing the Post Anaesthesia Care Unit (PACU). With the increased emphasis on early discharge after surgery and anaesthesia, the recovery of patients following surgery is usually assessed at two levels, PACU guided by BIS, and ambulatory surgical unit decided by Modified Aldrete Scoring (MAS) System.[2] Present study was done to compare the combination of ketamine-propofol versus fentanyl-propofol for day care urological surgeries to choose the better one with respect to time taken to achieve BIS less than 65, adequacy of sedation (using BIS), dose of propofol required, haemodynamic and respiratory parameters and recovery time (time to achieve MAS>8)

Materials and Methods

This prospective randomized double blind study was conducted after takingapproval from ethical committee and written informed consent from every patient. A total of 140 patients of age between 18-60 years, and American Society of Anaesthesiologists (ASA) Grade I & II scheduled for minor urological procedures on day care basis with normal renal and liver function were randomised using computer generated random number and were divided into two equal groups Group KP (n=70)which were given ketamine in dose of 0.5mg/ kg body weight as intravenous(IV) slow injection over 30 seconds followed by propofol given in the dose of 1mg/ kg body weight IV slowly and Group FP (n=70) given fentanyl citrate in dose of 1 µg/ kg body as IV slow injection followed by propofol given in the dose of 1mg/ kg body weight IV slowly. Procedures requiring more than half an hour and patients with hypertension, cardiac disease & heart blocks, morbidly obese (Body Mass Index >35), diabetic, sedatives, narcotics or alcohol abusers, taking psychotropic drugs, allergic to either propofol, ketamine and fentanyl or having any psychiatric illness were excluded from the study. One day prior to surgery patients were interviewed and assessed systematically, informed about nature of study and related complications. On arriving to the

operation theatre, non-invasive blood pressure, pulse oximetry (SpO_2), electrocardiogram leads and BIS sensor leads were attached to the patient and preoperative parameters like Heart Rate (HR), mean blood pressure (MAP), respiratory rate (RR) & oxygen saturation (SpO_2) and BIS score were recorded. Midazolam 1 mg IV was given as premedication after establishing IV access and ringer lactate 10ml/kg was infused before procedure & continued intraoperative at rate of 2ml/kg/h. Syringes of the study drugs were prepared immediately before surgery and labelled as syringe A and B by another person not involved in further part of study. Then either of the syringes was injected intravenously to the patients and after two minutes. Propofol was started 1mg/kg doses at the rate of 0.4 ml/sec. After getting the desired BIS (<65), surgical procedure was allowed to start. Thereafter, propofol was injected as intermittent dose of 10-20 mg bolus to maintain BIS (<65).The level of sedation was targeted BIS of 55-65 throughout the procedure. Patients were kept on spontaneous ventilation and 100% oxygen was given by bag and mask when SpO_2 fell below 90%.

All the vital parameters were recorded every third minute during and after the procedure until MAS >8 achieved. Any incidence of adverse effects like nausea, vomiting, apnoea, desaturation, bradycardia, hypotension, hypertension and hallucination was recorded. The patients were assessed for apnoea, which is defined as the loss of respiratory efforts for more than twenty seconds or fall of SpO_2 below 90%. It was managed with assisted ventilation using Bain's circuit with 100% oxygen. For bradycardia (HR< 60 beats per minute) atropine (10 µg/kg) and for hypotension (reduction of MAP < 20% of the baseline) mephentermine (0.1mg/kg) was used. Total duration of the procedure, total dose of propofol required during the procedure, recovery time (time from last bolus dose of propofol to achievement of Modified Aldrete Score > 8were recorded (Table 1). After completion of procedure patients were kept under close observation and vital parameters were recorded every third minute. Patient was shifted to the ward only if maintaining SpO_2 more than 95% on room air, haemodynamically stable and the Modified Aldrete Score was > 8.

Sample size of 140 with 70 patients in each group was determined with α=0.05, β=0.20, 80% power and 95% confidence limit. Data was compiled in the Microsoft Excel sheet, analysed using the SPSS IBM software version 21 (IBM SPSS advanced statistics; Chicago) and represented as Mean (± SD) for all quantitative variables. The frequency of all variables was displayed in charts and tables. Unpaired student 't' test and analysis of variance (ANOVA) test was applied for comparing quantitative data (mean) and Chi Square test was applied for qualitative data. Standard tests of significance were applied to determine the p value; the p value less than 0.05 were considered as statistically significant.

Results

Out of 153 patients counselled, 140 met the inclusion criteria and consented which were divided into two groups of 70 each, none left or was excluded from the study. Patients in both the groups were comparable and had no significant differences with respect to the age, sex, ASA grades, surgical procedures, and mean duration of surgery. Before induction parameters, i.e., HR, MAP, RR, SpO_2 and BIS were comparable and had no statistically significant difference so was time taken to achieve BIS 65 after giving propofol. The HR and MAP initially increased slightly though insignificantly in group KP ($p>0.05$) compared to pre induction value. In group FP the heart rate was in decreasing trend with the minimal value at ninth minute which was statistically significant ($p<0.002$) compared to pre induction value (as shown in Fig. 1). The difference in heart rate and MAP in both the groups was statistically significant ($p<0.05$) from third and twelfth minute and from third to fifteenth minute time interval respectively. In group FP the MAP decreased with the maximum decrease at ninth minute ($p<0.0001$) which was statistically significant compared to before induction value up to twelfth minute (as shown in Fig. 2). The RR increased intra operatively in group KP with the maximum rise at sixth minute which was statistically significant ($p<0.05$) compared to before induction value. In group FP maximum decrease RR at ninth minute ($p<0.0001$) which was statistically significant compared to before induction value (as shown in Fig. 3). The difference in both the groups were statistically significant ($p<0.05$) from third to fifteenth minute. There was a fall in SpO_2in both the groups and the difference between them was statistically significant ($p<0.05$) from third to twelfth minute (as shown in Fig. 4). In group KP five while in group FP nine patients required oxygen supplementation by bag and mask ventilation when saturation decreased below 90%.

The total amount of propofol consumed was higher in group FP in comparison to group KP (68.71±10.34 mg and 49.14±12.59 mg, respectively, $p<0.0001$) and it was statistically highly significant. The recovery (time required to achieve Modified Aldrete Score 8 from BIS value 65) occurred earlier in group FP in comparison to group KP (4.92±2.16 minute and 6.42±1.55 minute respectively, p value= <0.0001) and difference was statistically significant. The 8.57% patients from group FP had nausea post operatively compared to 4.28% in group KP. There was significantly early recovery in the FP group without any significant difference in the incidence of side effects of apnoea, hypotension, bradycardia and nausea-vomiting and hallucination between the groups (Table 2).

Table 1: Modified aldrete scoring system

Criterion	Score (Maximum Score: 10)	
Consciousness	Fully awake	2
	Aroused by verbal stimulus	1
	Not aroused by verbal stimulus	0
Breathing	Takes full breaths and can cough	2
	Takes only shallow breaths or has dyspnoea	1
	Cannot breath without assistance (apnoea)	0
Blood Pressure	Within 20 mm Hg of pre-op value	2
	20 to 50 mm Hg different from pre-op value	1
	≥50 mm Hg different from pre-op value	0
Oxygenation	>92% blood oxygen saturation(SpO_2)on room air	2
	Needs supplemental O_2 to maintain SpO_2>90%	1
	SpO_2 ≤90% on supplemental O_2	0
Motor Function	Can move all 4 extremities on request	2
	Can move 2 extremities on request	1
	Cannot move any extremities on request	0

Table 2: Comparison of various parameters between the two groups

Parameters Compared	Group KP (n=70)	Group FP (n=70)	P value
Time to achieve BIS Score <65 (mins)	3.03±0.120	3.09±0.19	0.862
Duration of surgery(min)	17.04±4.03	17.44±3.94	0.554
Amount of propofol (mg)	49.14±12.59	68.71±10.34	<0.0001*
Total time required to achieve MAS more than 8 (min)	6.42±1.55	4.92±2.16	<0.0001*
Incidence of nausea	3(4.28%)	6 (8.57%)	0.243
Incidence of fall in SpO_2 below 90%	5(7.14%)	9(12.85%)	0.398

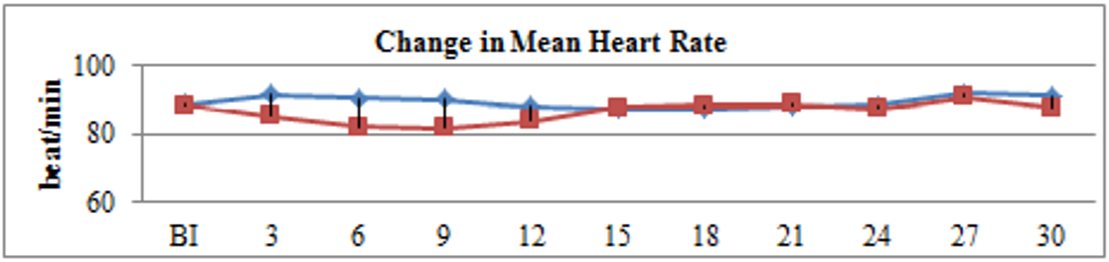

Fig. 1

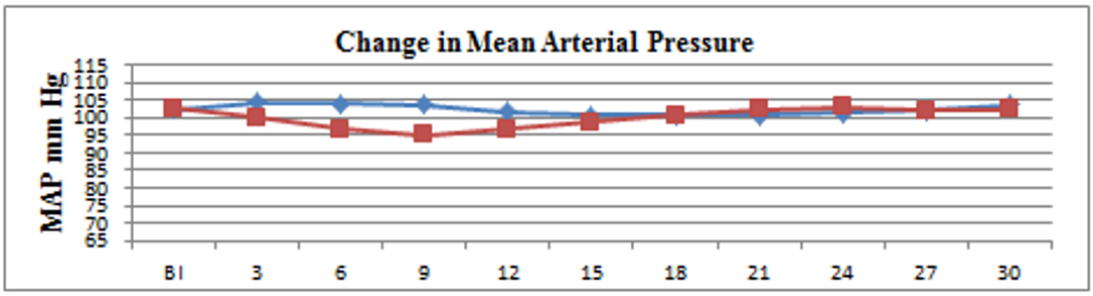

Fig. 2

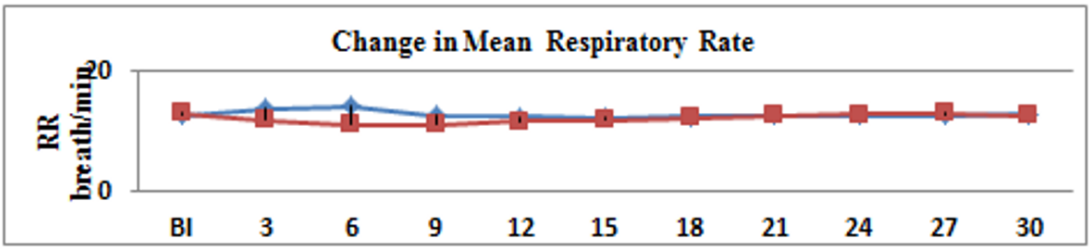

Fig. 3

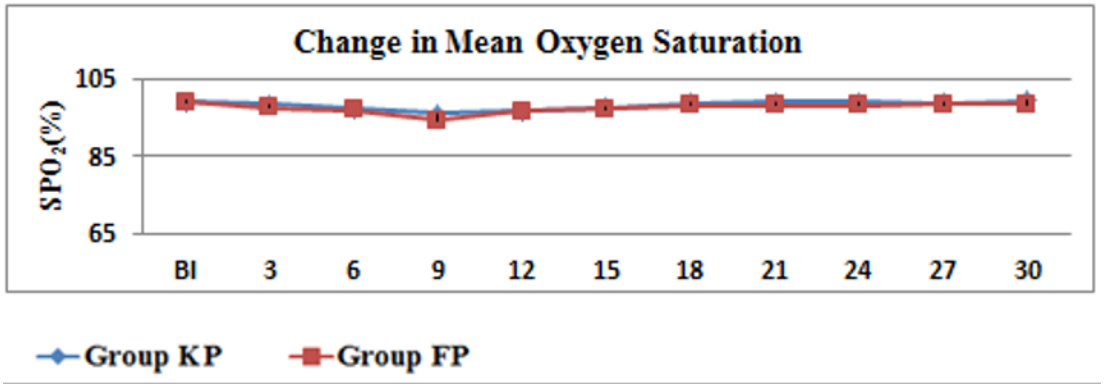

Fig. 4

Discussion

Present study revolved around evaluation of three drugs: ketamine, fentanyl and propofol, the former two given in fixed doses, followed by titrated doses of the latter while monitoring the level of sedation with BIS in range 55-65 keeping equal level of sedation and hypnosis and avoiding intraoperative awareness to compare requirement of propofol and recovery time assessing usefulness in day care surgery.[3] Propofol has emerged as the "gold standard" for day care surgery because of the superior recovery profile,[4] dual action as an induction and maintenance agent [5], direct antiemetic properties,[6] rapid and clear headed emergence from anaesthesia, and lack of cumulative effects even after prolonged administration. Ketamine is potent analgesic in sub anaesthetic dose and has gained attention in total intravenous anaesthesia with propofol because of its powerful analgesic action in doses and do not cause any myocardial and respiratory depression.[7] Recent studies have also shown that a combination of propofol and ketamine infusion was effective in decreasing opioid requirements without modifying recovery profiles for monitored anaesthesia care.[8] Moreover, ketamine may attenuate propofol induced hypoventilation and provide earlier recovery of cognition.[9] Fentanyl is a μ-opioid receptor agonist that produces profound dose dependent analgesia, reduces somatic and autonomic response to airway manipulation and provides haemodynamic stability.[10] Opioid interact synergistically with hypnotics for sedation and hypnosis[11] but cause significant respiratory depression and increase the incidence of postoperative nausea and vomiting (PONV).[12]

Patients given fentanyl showed decreasing trend of heart rate while it increased slightly though insignificantly post induction in patients anaesthetised with ketamine. Due to the inhibitory effect of propofol on baroreflexes and sympathetic activity, the effect of propofol on HR is variable with many studies showing decrease in HR.[3] The increase in HR in group KP can be attributed to the sympathomimetic activity of ketamine that causes increase in heart rate, which also counteract the myocardial depressant action of propofol, therefore, ketamine group had better haemodynamic stability with slight changes in HR[14] Fentanyl causes dose dependent reduction in HR by vagomimetic action and depress the cardiac conduction by direct membrane actions.[15] Carotid sinus baroreceptor reflex control of HR is markedly depressed by fentanyl.[16] Thus, in group FP, combination of propofol fentanyl leads to decrease in HR due to prevention of stress response by fentanyl and its myocardial depressing effect which is further enhanced by propofol.[17] The BP variables were more stable in ketamine-propofol group than fentanyl-propofol group. The stable BP in propofol- ketamine group could have been because ketamine causes sympathetic stimulation which tends to counterbalance the cardiovascular depressant effects of propofol. Ketamine stimulates the cardiovascular system and is associated with increase in BP, HR and cardiac output; these changes are not related to the dose of ketamine.[18] The combination of propofol with fentanyl was a particularly potent stimulus for hypotension.[15] The decrease in BP in the propofol- fentanyl group could be because of the cumulative cardio-depressant effects of propofol and fentanyl.[19-21]

Propofol is a profound respiratory depressant and apnoea usually occurs after an induction dose of propofol and its onset is usually preceded by marked tidal volume reduction and tachypnoea.[13] While ketamine had minimal effect on central respiratory drive although rapid IV bolus

administration or combination with opioid occasionally produces apnoea.[16] The incidence of prolonged apnoea by propofol is increased further by addition of an opiate either as a premedication or just before induction of anaesthesia.[13] Although apnoea may be relatively uncommon after midazolam, it depresses the ventilatory response to carbon dioxide. There are more documentations of significantly lower respiratory rate after induction in group fentanyl-propofol[22] while some observed no significant change in RR in ketamine-propofol group in comparison to fentanyl-propofol group.[23] The central respiratory depressant action of propofol causes apnoea that leads to fall in SpO_2 in the both groups further enhanced by fentanyl since it is an opioid respiratory depressant.[21,24] In obese patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) fall of SpO_2 and transient desaturation were observed to be more significant in the fentanyl-propofol than ketamine-propofol group.[25] Studies have revealed shorter recovery time /better wakefulness in group FP and late return of voluntary movements in KP group attributable to shorter duration of action and rapid clearance of fentanyl as compared to ketamine.[17,19,26,27] With fentanyl there was significantly higher intraoperative consumption of propofol to maintain BIS less than 65 or Ramsay Sedation Scale (RSS) Score of 5 in similar studies comparing same two drug combinations in patients undergoing elective upper gastrointestinal endoscopy, ERCP respectively[22,25,28] resulting in stable haemodynamics and deeper sedation though with low dose of propofol in patients with ketamine-propofol combination.

Overall patients remained stable with nil incidence of bradycardia, hypotension, hypertension, hallucinations or apnoea in either group. Although slightly higher incidence of nausea was observed in patients receiving fentanyl which may be due to the central emetic effects of fentanyl[14,15,24] but, as a whole, lower incidence of nausea and no incidence of vomiting are attributed to the antiemetic effect of propofol. Propofol has been used successfully to treat postoperative nausea in a bolus dose of 10 mg and has been successfully used to treat refractory PONV. This is all the more important at low doses and we have used propofol in low doses in this study.

Conclusion

We have concluded from the present study that, low-dose ketamine-propofol combination (ketamine 0.5 mg/kg with propofol 1 mg/kg) provides early sedation, more haemodynamic and respiratory stability, and the combination produces rapid anaesthesia with lesser untoward respiratory effects and only minor haemodynamic effects. BIS monitoring optimize intraoperative condition with minimum doses of propofol and leads to significantly early recovery for faster home readiness in the ambulatory surgery in both the groups. Overall, it may be concluded that ketamine-propofol combination is an appropriate choice when haemodynamic stability is of greater importance while fentanyl-propofol combination has advantage of faster recovery in day care settings.

Conflict of Interest: None.

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