Original Article

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Anaesthesia Section

Comparing Propofol-Ketamine and Propofol-Fentanyl as Procedural Sedation and Postoperative Analgesia for Total Intravenous Anaesthesia in Adult Patients Undergoing Short Surgical Procedures- A Randomised Clinical Study

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ABSTRACT

Introduction: Total Intravenous Anaesthesia (TIVA), an immensely popular procedure of recent times is most often conducted using propofol as the main anaesthetic agent. Ketamine or fentanyl has also been regularly used to compliment with their analgesic action, which propofol lacks.

Aim: To compare the induction characteristics, maintenance of anaesthesia, awakening and recovery characteristics while performing TIVA with either propofol-ketamine or propofol-fentanyl combinations.

Materials and Methods: This randomised, single blinded study was conducted, from March 2020 to August 2021, in a tertiary care centre of Kolkata, India. Total of 76 patients of either sex, aged between 18-45 years with an American Society of Anaesthesiologist (ASA) physical status I and II, who were posted for short surgical procedures, with a duration of surgery less than 30 mins were equally divided into two groups. Group A received propofol ketamine (1:1), prepared by mixing 4 mL ketamine (50 mg/mL) with 20 mL of 1% Propofol (10 mL/kg), while group B received propofol-fentanyl solution (1:1) was prepared by mixing 4 mL (50 µg/mL) of fentanyl with 20 mL of 1% propofol (10 mg/mL). Induction was done with ketamine 10 mg/kg+propofol 1 mg/kg in group A and fentanyl 1.5 µg/kg+propofol 1.5 mg/kg while maintenance of anaesthesia was achieved with continuous infusion of the prepared solutions for either group, respectively at a rate of around 20 mL/hour or more, as per required to maintain the Ramsay Sedation Scale (RSS) score of 6. Intraoperative haemodynamic parameters, including respiratory rates, awakening time, recovery time and the possible the side-effects were recorded at regular intervals. Student's t-test was used for quantitative data and Chi-square test for qualitative data. A p-value of less than 0.05 was considered statistically significant.

Results: Patients of group B developed significantly more incidents of bradycardia (20 in group B and 3 in group A) and hypotension (28 in group B and 2 in group A). Respiratory depression was also significantly more in group B (p-value <0.005). However, recovery, awakening, VAS score and other side-effect profiles were all comparable in the two groups.

Conclusion: Propofol-ketamine provides equipotent analgesia with better haemodynamic control and minimal side-effects in comparison to propofol-fentanyl while used in TIVA for adult patients undergoing short surgical procedures.

Keywords: Day-care surgery, Hypotension, Visual analog score

INTRODUCTION

Total Intravenous Anaesthesia (TIVA) has gained immense popularity in recent times owing to the gradually increasing practice of office based and day-care surgical procedures. TIVA is popularly used for short surgical procedures including day-care surgeries. The advantages include reduced incidence of postoperative nausea and vomiting, more predictable and rapid recovery, greater haemodynamic stability, preservation of hypoxic pulmonary vasoconstriction and reduced risk of organ toxicity, thereby allowing early patient discharge [1,2]. TIVA can also be used in some cases where the administration of inhaled anaesthetics is impossible or in conditions where traditional anaesthetic delivery systems may be unavailable or impractical.

At present times, TIVA is generally delivered using combination of several short or ultra-short acting drugs, each of which has their individual, specific effects to provide balanced anaesthesia [3]. The commonly used drug for this purpose includes short-acting benzodiazepines, propofol, short acting opioids like fentanyl, ketamine etc. This is mainly because no sole anaesthetic agent has shown to have all the requisite properties to fulfil an ideal agent for procedural sedation. However, a combination of these drugs can be effectively used to provide adequate hypnosis, amnesia and analgesia, which are the sole components of a balanced anaesthesia [3].

Propofol, though popular among certain outpatient procedures, because of its short duration of action and antiemetic, amnestic, anticonvulsant and antipruritic properties, it does not cause analgesia [4]. Hence, when used for TIVA, it is given along with some potent analgesics like ketamine or fentanyl [5]. Ketamine provides excellent analgesia and also aids to maintain the haemodynamic stability when used with propofol. It can also decrease the pain of propofol injection by its local anaesthetic effects [6-8]. Similarly, Fentanyl also has a rapid onset and short duration of action, thus when used as an analgesic with propofol can lead to reduction of dose and thereby, complications related to propofol [9].

Studies have shown that ketamine-propofol combination provides a better option than propofol-fentanyl combination while giving TIVA [2,10-12]. However, owing to the advantages and overall usage in day-to-day practice, there is always a scope to do further research to compare the efficacies of ketamine and fentanyl when used with propofol for providing TIVA.

This study was conducted to evaluate and compare the efficacy of propofol-ketamine and propofol-fentanyl combinations for TIVA in adult patients undergoing short surgical procedures. The induction characteristics, maintenance of anaesthesia and awakening and recovery characteristics following anaesthesia by the two combinations were primarily studied. Along with that, incidences of any adverse effects were also noted as a secondary study outcome.

MATERIALS AND METHODS

This randomised, single blinded clinical study was conducted, from March 2020 to August 2021, in a tertiary care centre of Kolkata, India.The approval from the Institutional Ethics Committee was obtained [No/NMC/681 dated 10/02/2020].

Inclusion criteria: A total of 76 patients of either sex, aged between 18-45 years of age with an ASA physical status I and II, who were posted for short surgical procedures, with a duration of surgery less than 30 mins (like fibroadenoma of breast excision, circumcision, dilatation and curettage, dilatation and evacuation etc.) that require TIVA were included in the study.

Exclusion criteria: Patients refusing to participate in the study, having Basal Metabolic Index (BMI) >35 kg/m^2, known allergy or contraindications to either study drugs, patients with head injury, seizure disorder, congestive cardiac failure, haemorrhagic disorder, chronic kidney diseases or neurological disorders were excluded from the study.

Sample size calculation: PS Power and Version 2.1.30, February 2003, was used for sample size calculation. Sample size was calculated taking a difference of wake fulness or recovery score of 0.20 as clinically acceptable margin [3]. Sample size thus, required in either arm was estimated to be 34. Taking a 10% attrition, the study subjects recruited in each arm was 38.

Study Procedure

After taking written informed consent from the patients and a detailed preanaesthetic check-up, the patients were randomly divided into two equal groups, each comprising of 38 patients, by opening sealed envelopes.

After receiving the patients in the operation theatre, monitors were attached and an intravenous cannula of 18G secured, following which the patients were preloaded with Lactated Ringer's Solution @10 mL/kg body weight. All the patients in either of the groups were given supplemental oxygen flow at the rate of 6L/min via face mask and were then premedicated with injections of glycopyrrolate 0.2 mg, midazolam 0.03 mg/kg and ondansetron 4 mg intravenous 2 minutes before induction.

In a single 50 mL syringe, a mixture of propofol-ketamine or propofol-fentanyl was prepared by using an aseptic technique for delivery via an infusion pump. In case of group A (n=38), a propofol-ketamine solution (1:1) was prepared by mixing 4 mL ketamine (50 mg/mL) with 20 mL of 1% propofol (10 mL/kg), a total of 24 mL of solution. In case of group B (n=38), a propofol-fentanyl solution (1:1) was prepared by mixing 4 mL (50 µg/mL) of fentanyl with 20 mL of 1% propofol (10 mg/mL), a total of 24 mL. Induction was done with ketamine 10 mg/kg+propofol 1mg/kg in group A and fentanyl 1.5 µg/kg+propofol 1.5 mg/kg and achievement of induction in both the groups were considered with a Ramsay Sedation Scale (RSS) of 6. In both groups, maintenance of anaesthesia was achieved with continuous infusion of the prepared solutions for either group respectively at a rate of around 20 mL/hour or more, as per required to maintain the RSS score of 6.

Haemodynamic parameters and RSS were observed continuously and recorded at intervals of every five minutes during operation. Neither any muscle relaxant was used nor the patients were intubated. After completion of the surgery or end of the skin closer depending on the type of surgery, infusion was stopped and patients were transferred to the recovery room, Postanaesthesia Care Unit (PACU) with oxygen support at the rate of 6L/min and vitals were monitored for one hour. Duration of surgery, awakening time (define das the time from the first administration of the drug to the opening of eyes to verbal commands after surgery). Total sedation time (awakening time) was defined as the time, from the first administration of the drug to the opening of eyes to verbal commands after surgery. Recovery time was defined as the time taken from stopping the infusion of the study drug to the point when the patients will achieve a Modified Aldrete Score of more than or equal to 8 [13]. After ensuring a modified Aldrete score ≥8 patients were shifted to the surgery ward. Postoperative analgesia is assessed by Visual Analogue Scale (VAS).

STATISTICAL ANALYSIS

Statistical Package for Social Sciences software version 20.0 (IBM) was used for statistical analysis and descriptive analysis was done in the form of proportion for categorical variables, mean [Standard Deviation (SD)] or median {Interquartile range (IQR)} for continuous variables. Data were checked for normal distribution using tests (Shapiro-Wilk normality test) for normality and parametric or non parametric test was performed accordingly. Student's t-test was used for quantitative data and Chi-square test for qualitative data. A p-value of less than 0.05 was considered statistically significant.

RESULTS

[Table/Fig-1] shows that the age and sex difference with ASA distribution were similar.

[Table/Fig-2] shows that the time of awakening and difference of recovery time among the two groups were not statistically different, although both were slightly more among group B. The postoperative pain score was less among the patients of group A than group B, although it was not statistically significant.

Parameters		Group A (n=38)	Group B (n=38)	p-value
Age (in years) (Mean±SD)		27.16±7.59	27.32±5.66	0.502
Gender	Male	14	15	0.813
	Female	24	23	
ASA	I	22	23	0.796
	II	16	15	

[Table/Fig-1]: Distribution of study subjects according to age, gender and ASA status.
ASA: American society of anaesthesiologist

Criteria	Group A (n=38)	Group B (n=38)	p-value
Time of awakening (min)	23.68±3.35	24.34±2.66	0.521
Recovery time (min)	27.82±3.58	29.26±3.19	0.084
VAS Score	0.32±0.47	0.45±0.50	0.241

[Table/Fig-2]: Distribution of study subjects according to time of awakening, recovery time and postoperative VAS score.

[Table/Fig-3-5] show that the mean heart rate, systolic blood pressure, respiratory rate was significantly more among the subjects of group A than group B.

Time (minutes)	Heart rate (beats/min)		p-value
	Group A	Group B	
1	81.55±8.42	76.21±7.17	0.007
2	77.82±8.45	70.32±7.23	<0.001
3	75.08±8.02	64.45±6.97	0.001
4	72.95±8.78	61.18±5.10	<0.001
5	71.68±8.85	60.37±5.10	0.001
10	72.45±8.30	65.05±4.01	<0.001
15	74.79±7.78	68.89±3.68	<0.001
30	79.92±8.06	73.26±4.51	0.001

[Table/Fig-3]: Distribution of heart rate among the patients (n=38).
A p-value of less than 0.05 was considered statistically significant

Time (minutes)	Systolic blood pressure (mmHg)		p-value
	Group A	Group B	
1	122.63±8.04	118.26±6.84	0.030
2	120.55±8.51	112.47±7.06	<0.001
3	117.18±8.93	106.03±6.50	0.001
4	115.87±7.84	102.97±6.56	<0.001
5	114.87±6.85	103.21±5.93	<0.001
10	115.89±7.30	106.97±5.31	0.001
15	117.97±6.73	110.97±5.23	<0.001
30	121.97±6.57	116.24±5.87	0.001

[Table/Fig-4]: Distribution of Systolic Blood Pressure (SBP) among the patients (n=38). A p-value of less than 0.05 was considered statistically significant

Time (minutes)	Respiratory rate (breath/min)		p-value
	Group A	Group B	
1	14.11±0.95	12.58±0.75	<0.001
2	12.84±0.85	12.08±0.85	0.001
3	12.45±0.95	11.32±0.66	<0.001
4	11.97±0.78	11.11±0.45	<0.001
5	11.92±0.67	11.26±0.64	<0.001
10	12.66±0.90	11.87±0.57	0.001
15	13.34±0.87	12.47±0.60	<0.001
30	14.37±0.91	13.39±0.49	0.001

[Table/Fig-5]: Distribution of Respiratory rate (RR) among the patients (n=38). A p-value of less than 0.05 was considered statistically significant

[Table/Fig-6] shows that the occurrence of hypotension and bradycardia were statistically more among the subjects of group B than group A patients. However, the occurrence of nausea among both the groups was similar.

Criteria	Group A n (%)	Group B n (%)	Total n (%)	p-value
Hypotension	02 (5.3)	28 (73.7)	30 (39.5)	<0.001
Bradycardia	03 (7.9)	20 (52.6)	23 (30.3)	<0.001
Nausea	01 (2.6)	02 (5.3)	3 (3.9)	0.556

[Table/Fig-6]: Distribution of study subjects according to hypotension, bradycardia and nausea (n=38). A p-value of less than 0.05 was considered statistically significant

Among the other side-effects, there was no complication like emergence reaction, agitation, increased oral secretions in this study and only one patient in group A and two in group B had nausea but no vomiting.

DISCUSSION

Total Intravenous Anaesthesia (TIVA), the anaesthestic procedure of choice for short surgical procedures, is generally conducted using propofol based anaesthesia. However, due to lack of its analgesic property, several other drugs have been used as supplemental analgesic, among which ketamine and fentanyl are most commonly used. Few studies have shown propofol-ketamine having a better result than propofol-fentanyl though a definitive conclusion needs further research [2,10-12].

This study was thus done to compare the induction, maintenance of anaesthesia, awakening and recovery characteristics following anaesthesia with propofol-ketamine and propofol-fentanyl combinations for TIVA by studying the incidences of any adverse effects in adult patients undergoing short surgical procedures.

In the present study, continuous infusion of propofol-ketamine (group A) and propofol-fentanyl (group B) were used to maintain a steady state sedation level, by achieving a RSS of 6. Intraoperatively, there was not much difference among the total dose of drugs required in either of the groups to maintain a steady state level. Similarly, awakening time, recovery time among the patients of either group were also found to be non significant.

However, regarding haemodynamics, heart rate was found to significantly reduced in group B (after achieving RSS6) at 1 minute, 2 minutes, 3 minutes, 4 minutes, 5 minutes, 10 minutes, 15 minutes; whereas the Systolic Blood Pressure (SBP) also showed significant decrease in patients of group B at those same time intervals. Respiratory Rate (RR) started decreasing more at group B and became statistically significant (p-value <0.05) at 1 minute, 2 minutes, 3 minutes, 4 minutes, 5 minutes, 10 minutes, 15 minutes, 30 minutes as well in this study.

Tajoddini S and Motaghi M, compared the sedative, analgesic effects as well as safety characteristics of ketamine-propofol and fentanyl-propofol combinations in painful emergency procedures [10]. They found that the ketamine-propofol group provided superior analgesia and sedation with faster recovery and lesser adverse events in comparison to the fentanyl-propofol group.

Reddy BAP et al., compared the intraoperative haemodynamic responses as well as postoperative spontaneous eye opening and PONV after injection of propofol-ketamine and propofol-fentanyl in 100 patients undergoing short surgical procedures under TIVA [11]. They concluded that haemodynamic responses were better in propofol-ketamine group with lesser adverse effects, though patients in propofol-fentanyl had superior postoperative recovery.

El-Rab NAG et al., made a comparative study between propofol-ketamine and propofol-fentanyl combinations in paediatric patients undergoing upper gastrointestinal endoscopy [12]. They studied 60 children aged 6-12 years and concluded that propofol-ketamine provided better haemodynamic stability with comparable recovery and adverse effect profiles.

Sharma R et al., did a randomised, double-blind study on 100 adult patients, giving slow bolus of premixed injection of either ketamine-propofol (1 mg/kg) or fentanyl-propofol (1.5 mg/kg) followed by TIVA infusion to a predetermined sedation level using RSS for short orthopaedic procedures [2]. They reported a significant decrease (p-value <0.001) in the pulse rate, systolic and diastolic blood pressure in intraoperative and postoperative period in group 2 (fentanyl propofol group) whereas there was significant rise in pulse rate, systolic and diastolic blood pressure in group 1 (ketamine-propofol group). Respiratory depression was more pronounced in group 2. Mean total sedation time as well as recovery time was significantly prolonged in group 2 compared to group 1.

Kurdi MS et al., conducted a prospective randomised double-blind study among 60 adult females scheduled for elective tubal sterilisation by minilaparotomy in which the patients received a slow bolus injection followed by Ketofol containing ketamine: Propofol (1:1) (group A), ketamine: propofol (1:2) (group B), and fentanyl: propofol (group C) to a predetermined sedationlevel using RSS [14]. Considering the onset of sedation, intraoperative sedation score, and recovery time, group C (fentanyl-propofol) patients were less sedated than counter parts in group A and B. Considering the verbal rating scale for pain postoperatively, group C patients had poor analgesia compared to group A and B. They found that ketamine-propofol provides better sedation level, better haemodynamic and respiratory stability compared to fentanyl-propofol.

Similarly, Akhondzadeh R et al., in their study, comparing the effects of propofol-fentanyl with propofol-ketamine to sedate patients under going endoscopic retrograde cholangiopancreatography outside the operating room, found that the lower amount of pain and apneain propofol- ketamine group [15].

In another study done by Singh Bajwa SJ et al., propofol-fentanyl combination produced a significantly greater fall in pulse rate and in both systolic and diastolic blood pressures as compared to propofol-ketamine during induction of anaesthesia [3]. Propofol-ketamine

combination produced stable haemodynamics during maintenance phase.

Similar findings were also found in studies done by Tosun Z et al., Goyal R et al., Nalini KB et al., Khutia SK et al., in all of which haemodynamic status were found to be well maintained in ketofol group with equally acceptable anaesthesia, recovery, analgesia and side-effect profiles [16-19]. The findings of all these studies thus corroborate with the findings of this present study.

Limitation(s)

This was a single centre study carried out in a tertiary care hospital. The population did not include the paediatric and geriatric population and the ASA III and IV patients, where the efficacy and safety may vary.

CONCLUSION(S)

Thus, from this study we can well conclude that ketamine when combined with propofol can provide better analgesia with adequate haemodynamic stability and minimal side-effects in comparison to Fentanyl during procedural sedation in adult patients undergoing short surgical procedures. Therefore, propofol-ketamine combination provides us with a perfect option for providing TIVA, particularly in daycare procedures.

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