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Original Research Article

Comparative Study between Intravenous Ketamine-Propofol and Intravenous Fentanyl-Propofol for Procedural Sedation and Analgesia in Paediatric Patients undergoing Short Surgical Procedures

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Conflict of interest: Nil

Abstract

Background: Paediatric patients present with a number of painful conditions that require immediate interventions. The ability to provide safe and effective analgesia is the foremost responsibility of an anaesthesiologist. Additionally, sedation is advantageous in a paediatric patient. With availability of new sedative and hypnotic agents, improved day care anesthesia in paediatrics has become very popular.

Methodology: The present study was conducted as a comparative, prospective observational study in the Department of Anaesthesiology at a tertiary care centre, Bhopal. Sixty patients aged between 4-10 years with ASA grade I and II undergoing short surgical procedures for Procedural sedation and analgesia were included in this study. Group 1 received 2ml of normal saline (pre-induction) and calculated volume of drug from 11ml of Ketamine-Propofol solution for induction while Group 2 received Fentanyl 1.5 microgram/kg diluted to 2 ml with normal saline (preinduction) and calculated volume of drug from 11ml of Propofol solution for induction. In both groups, the initial bolus dose of the intravenous solution 1mg/kg i.v. was followed by adjusted infusion at the rate of 50 microgram/kg/min to achieve a Ramsay sedation scale score of six. Procedural sedation and hemodynamic variations was the primary outcome.

Statistical Analysis: All observations SPSS ver. 20 software and p value < 0.05 was considered to be statistically significant.

Results: Mean arterial pressure (MAP) decreased in both the groups after induction as well as during the intra operative period, but the decrease was much more significant in Group 2. There was a statistically significant difference in Ramsay Sedation Score (RSS) between two groups (p value < 0.05).

Conclusion: Ketamine-Propofol infusion was found to be superior and safer regimen than Fentanyl-Propofol infusion in terms of hemodynamic stability, sedation and analgesia in paediatric patients undergoing short surgical procedure

Keywords: Procedural sedation, paediatric, propofol, fentanyl, ketamine, Ramsay sedation score

Introduction

Paediatric patients present with a number of painful conditions that require immediate interventions. The ability to provide safe and effective sedation and analgesia is the foremost responsibility of an anaesthesiologist. Paediatric patients are more prone to suffer from anxiety and pain, they benefit universally if provided with sedation and analgesia both, during surgical procedure and post operatively too. This also prevents pain sensitization in these patients. With availability of new sedative and hypnotic agents and analgesic drugs, improved day care anesthesia has become very popular [1,2].

The history of paediatric sedation is not well documented in the literature. It is not "contained" in any one professional area of study. However, children have always required anesthesia and sedation for a variety of procedures whether therapeutic, diagnostic or surgical procedures.

Procedural sedation and analgesia is defined as a state in which there is minimally depressed level of consciousness, patient can keep a patent airway independently and respond to bodily stimulation and verbal commands appropriately. Deep sedation is defined as a controlled state of depressed consciousness in which the patient is not easily arousable. There may be partial or complete loss of protective reflexes, including the ability to maintain a patent airway independently by the patient. General anesthesia is a controlled state of unconsciousness in which there is loss of protective reflexes, loss of the ability to maintain a patent airway, loss of the ability to respond to verbal commands and physical stimulation [3,4].

An ideal agent for procedural sedation and analgesia should provide sedation, analgesia, maintain haemodynamic stability, have a short half-life, not associated with unpleasant emergence reaction and should have minimal interaction with other drugs . No particular drug has all these features, therefore a mixture of drugs with changeable doses are nowadays being used to achieve these goals.

Ketamine may be used as a sole anaesthetic agent or mixed with other drugs. It has the advantages of "Dissociative anaesthesia", maintains cardiovascular stability and is a bronchodialator. Disadvantages include emergence reactions, raised intracranial, intraocular pressures and nausea and vomiting

Propofol is a short acting drug with rapid and smooth induction and recovery, good antiemetic action that reduces the incidence of PONV. Disadvantages include pain on injection and dose dependant decrease in mean arterial pressure and respiratory depression,

Fentanyl is a synthetic opioid mainly used for its analgesic properties. Various studies have revealed that addition of Fentanyl to Propofol decreases the requirement of either drug but the risk of attenuation of airway reflexes and respiratory depression is increased. The combination of Ketamine and Propofol would be synergistic, allowing a reduction in dose requirement of each other. with Ketamine providing good analgesia and Propofol for sedation [5,6].

Nowadays different combinations of drugs are used for sedation and analgesia. This study was undertaken to compare the effectiveness between intravenous Propofol along with Ketamine and intravenous

Propofol along with Fentanyl for Procedural sedation and analgesia in paediatric patients undergoing short surgical procedures. In our study we used Ramsay Sedation Score as a tool for comparing the sedation and analgesia in paediatric patients

Materials and Methods

After approval from Ethics committee of the institute, and informed consent by parents, 60 patients aged between 4-10 years with ASA grade I and II undergoing short surgical procedures like Reduction of fracture dislocations, Incision and drainage of abscess, debridement and dressing and of wounds, Burn dressing changes, Herniotomy were included in this prospective, comparative study.

The exclusion criteria were known allergy or contraindication to any drug, head injury, seizure disorder, psychological disorder and full stomach patients. All the selected patients fulfilling the inclusion criteria were enrolled and were randomly allocated into two groups of 30 patients each by chit-in-the-box method.

Group 1: received 2ml of normal saline (pre-induction) and calculated volume of drug from 11ml of Ketamine-Propofol solution for induction. **Group 2:** received Fentanyl 1.5 microgram/kg diluted to 2 ml with normal saline (preinduction) and calculated volume of drug from 11ml of Propofol solution for induction

For Group1, Propofol Ketamine solution (1:2) was prepared by mixing 1 mL Ketamine (50 mg/ mL) with 10 mL Propofol 1% (10 mg/mL) such that each mL of the Propofol-Ketamine solution would contain rounded off to 9 mg of Propofol and 4.5 mg of Ketamine, respectively. For Group 2, Propofol-Fentanyl , 10 mL Propofol 1% was mixed with 1 mL of normal saline such that each mL contained 9.0909 mg of Propofol (rounded off to 9 mg/mL).

Preoperatively patients were evaluated by taking detailed clinical history, elicited from the parents and older patients themselves, general physical and systemic examination. Informed consent was taken from parents after explaining risks, benefit, objective and outcome of the study. After confirmation of NPO status, patients were taken in the operation theatre and a peripheral venous access was secured via 22G i.v. cannula. Patients were then monitored for vital signs: NIBP, pulse rate, respiratory rate, pulse oximetery and ECG. For premedication, intravenous Inj. Ranitidine (1mg/kg), inj. Metoclopramide (0.15mg/kg) and inj. Glycopyrolate (0.01mg/kg) was slowly given 10 min before starting the procedure.

In both groups, the initial bolus dose of the intravenous solution 1mg/kg i.v. was followed by adjusted infusion at the rate of 50 microgram/kg/min to achieve a Ramsay sedation scale score of six. Patients were connected to oxygen via facemask.

The sedation level was assessed at every 5 min interval and the infusion rate was adjusted accordingly with a backup plan to achieve a Ramsay Sedation Score (RSS) [Figure 1] of 6. Heart rate and NIBP were measured before induction (baseline), after induction and then at every 5-min interval till the completion of the procedure and postoperatively in the recovery room. Throughout the perioperative period oxygen saturation was continuously monitored. Desaturation was defined as 10% decrease in SpO_2 when compared with baseline. Apnoea was considered with cessation of respiration for 15 s or more, and was managed by assisting ventilation. When the mean arterial pressure (MAP) dropped by >20% of the baseline, hypotension was considered, and was managed accordingly by fluid bolus or vasopressors. Bradycardia was considered with heart rate less than 60 beats/min and was managed with atropine 20 mcg/kg iv. Any movement of the patient or changes in vital parameters suggestive of

pain was treated with increase in the infusion rate of the drugs under study. The recovery time which was defined as the time from discontinuation of infusion of the study drug and achievement of RSS score of 3 was noted. Patients were then shifted to the recovery room.

Statistical Details

All the data analysis was performed using SPSS ver. 20 software. Frequency distribution and cross tabulation was used to prepare the tables. Quantitative data is expressed as mean±standard deviation, whereas qualitative data is expressed as percentage. The two-sample student "t–test" was used to compare between group comparisons like age, weight, mean arterial blood pressure, heart rate, respiratory rate, Spo2 while Chi-square test was used to analyze sex, ASA grade and adverse effects. P value < 0.05 was considered statistically significant.

Results

In our study both the groups were comparable demographically [Table 1]. There was statistically significant difference in MAP between the two groups. Although MAP decreased in both the groups after induction as well as during the intra operative period, the decrease was much more significant in Group 2 as shown in [Table 2 and Graph 1]. Mean RSS was almost same till 5 min after induction in both the groups. After 10 min significant difference was found between two groups. Deeper level of sedation was observed in Group1 as shown in [Table 3 and Graph 2] Thus there was a statistically significant difference in RSS between two groups (p value < 0.05). Incidence of side effects like hypotension and bradycardia were seen more in Group 2 while emergence reaction and PONV more in Group 1 as shown in [Table 4 and Graph 3]. Mean recovery time in Group 1 was 10.06±1.55 while in Group 2 was 8.36±1.66. It was observed that recovery time was significantly longer in Group 1 than in Group 2. Thus there was a statistically significant difference in recovery times between two groups as shown in [Table 5 and Graph 4].

Table 1: Demographic profile between two groups

Demographic variables	Group 1 (n=30)	Group 2(n=30)	P value
Mean age	8.06±1.87	8.13±1.96	0.89
Weight	19.1±3.44	19.13±3.8	0.97
ASA(I : II)#	19:11	20:10	0.07
M : F(Male : female)#	12:18	13:17	0.06
Type of surgery# (FD/BD/DW/ID/H)	9/5/5/6/5	7/5/5/7/6	>0.05

Data are expressed as mean ± standard variation except marked # which are categorical. FD- Fracture dislocations, BD- burn dressing changes, DW- Debridement of wounds, ID- incision and drainage of abscess, H- Herniotomy.

Table 2: Mean arterial pressure at various time intervals

MAP	Group 1		Group 2		P value
	Mean	SD	Mean	SD	
Baseline	77.36	3.55	76.27	4.1	0.27(NS)
After induction	69.13	3.37	63.06	4.48	<0.0001 (HS)
5 minute	70.93	3.61	64.03	3.37	<0.0001 (HS)
10 minute	70.23	3.58	65.53	4.07	<0.0001 (HS)
15 minute	70.13	3.75	64.3	3.31	<0.0001 (HS)
20 minute	70.16	3.35	63.4	4.08	<0.0001 (HS)

25 minute	68.06	1.70	64.36	3.34	0.0002 (HS)
30 minute	68.03	2.04	64.4	3.34	<0.0001 (HS)
35 minute	67.96	1.35	63.9	4.2	<0.0001 (HS)
Post operatively in recovery room	67.9	1.42	63.86	3.5	<0.0001 (HS)

Table 3: Ramsay sedation score at various time intervals

RSS (RAMSAY SEDATION SCORE)	Group 1		Group 2		P value
	Mean	SD	Mean	SD	
Baseline	1.23	0.43	1.33	0.47	0.39 (NS)
After induction	5.9	0.30	5.96	0.18	0.35 (NS)
5 minute	5.96	0.18	5.83	0.37	0.08 (NS)
10 minute	6	0.30	5.5	0.62	0.0002 (HS)
15 minute	5.96	0.18	5.26	0.98	0.0003 (HS)
20 minute	5.93	0.25	5.1	1.09	0.83 (NS)
25 minute	5.53	0.73	4.96	1.0	0.014 (HS)
30 minute	4.33	0.47	4.9	0.88	0.002 (HS)
35 minute	3.26	0.44	3.8	0.48	0.0001 (HS)
Postoperative in recovery room	2.4	0.49	2.6	0.49	0.11 (NS)

Table 4: Incidence of side effects between the groups

Side effects	Group 1		Group 2		P value
	N	%	N	%	
Hypotension	5	16.6	12	40	0.045(HS)
Bradycardia	0	0	6	20	0.031(HS)
Apnoea	0	0	0	0	NA
Emergence reaction	6	20	0	0	0.031(HS)
PONV	4	13.3	2	6.6	0.66(NS)

Table 5: Comparison of recovery time between two groups

Recovery Time	Mean	Standard Deviation	P Value
Group 1	10.06	1.55	0.0003 (HS)
Group 2	8.36	1.88	

Table 6: Ramsay Sedation Scale

1	Patient anxious or agitated or both
2	Patient cooperative , oriented and tranquil
3	Patient responds to command only
4	A brisk response to light glabellar tap or loud auditory stimulus
5	A sluggish response to light glabellar tap or loud auditory stimulus
6	No response to light glabellar tap or loud auditory stimulus

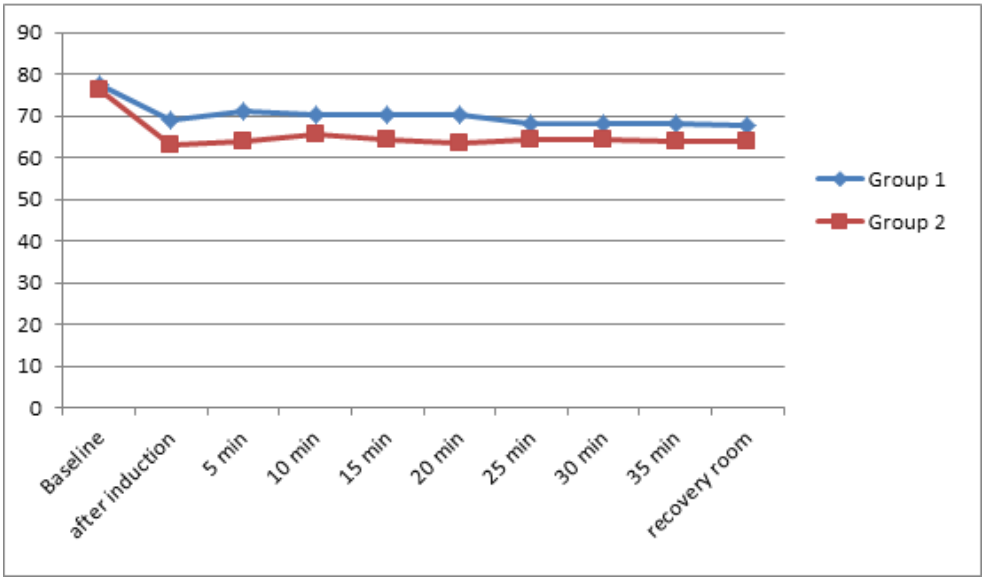

Figure 1: Mean arterial pressure at various time intervals

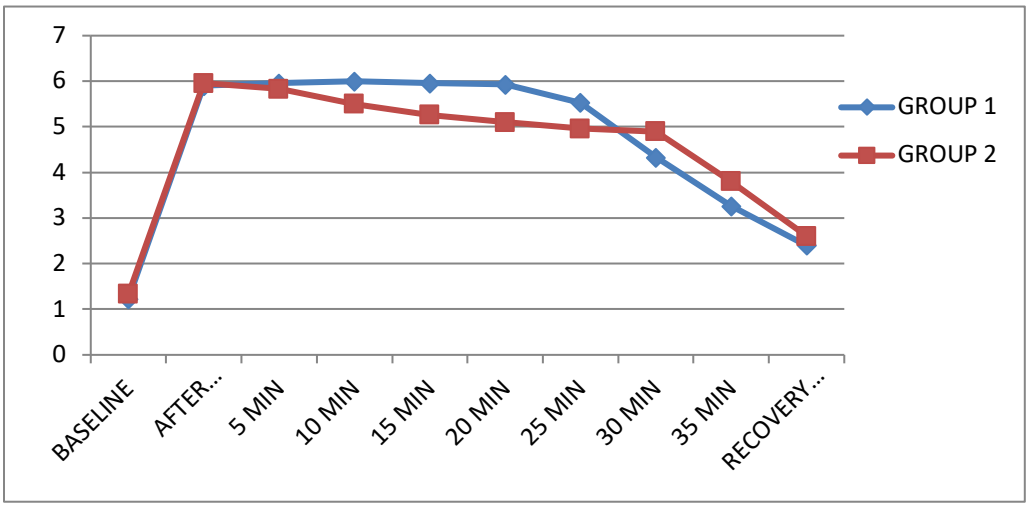

Figure 2: Ramsay sedation score at various time intervals

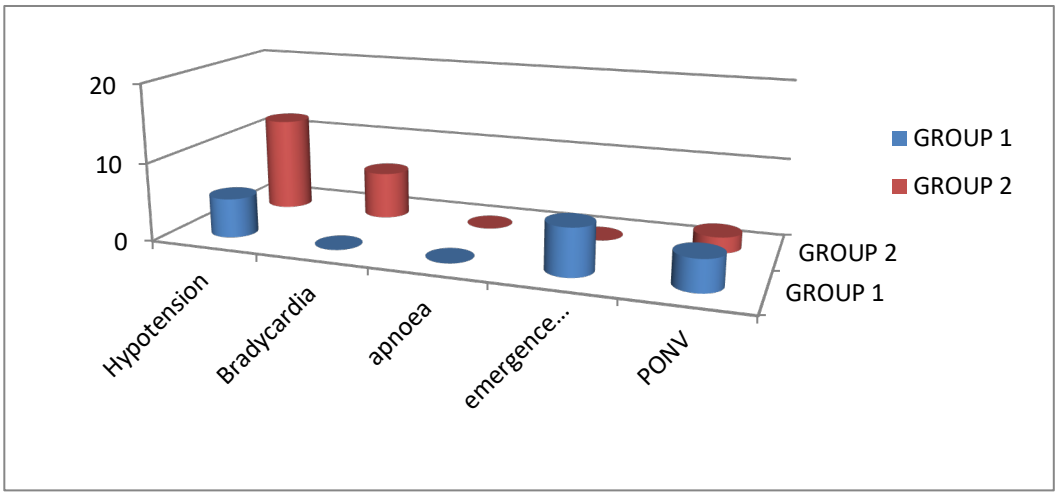

Figure 3: incidence of side effects between the groups

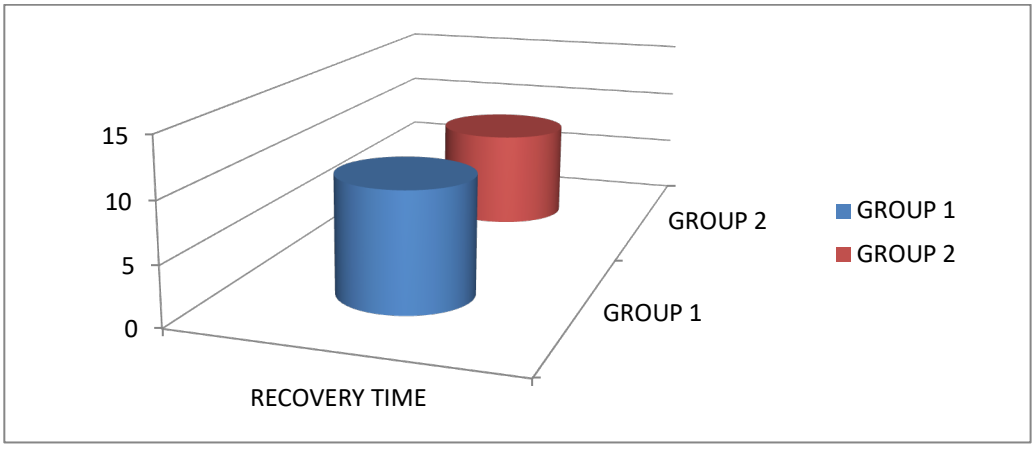

Figure 4: comparison of recovery time between two groups

Discussion

Painful procedures in children require adequate sedation and analgesia. To reduce anxiety and for optimizing procedural conditions for an uncooperative child optimum sedation is very useful. The ability to provide effective and safe sedation by an anesthesiologist improves patient outcome as well as parental satisfaction. There is not any single perfect or ideal agent that can provide balanced anesthesia that is amnesia, hypnosis and analgesia. Therefore in the quest in providing effective and safer sedation and analgesia, many studies have been undertaken using various combinations of sedative and hypnotic drugs in various doses.

In our study mean age of patients of Group 1 was 8.067± 1.87 years whereas mean age of Group 2 was 8.13± 1.96 years. Mean weight in Group 1 was 19±3.44 whereas in Group 2 was 19.13±3.8. In our study there were 40% males and 60% females in Group 1 while 43.3% males and 56.6% females in Group 2. The two groups were comparable for demographic variables such as age, gender, weight and type of surgery ($p>0.05$). In Group 1, MAP was 77.36±3.55 at baseline and it reduced to 67.9±1.42 post operatively in recovery room.

In Group 2, MAP was 76.27±4.1 at baseline which reduced to 63.86±3.9 in recovery room. Although MAP decreased in both the groups after induction as well as during the intra operative period, the decrease was much more significant in Group 2. Thus, there was statistically significant difference between two groups ($p<0.05$) in our study. Our findings were similar to study conducted by Akin A, Esmaoglu *et al* (2005) [7].

They compared the effects of Propofol and Propofol-Ketamine on hemodynamics, sedation level, and recovery period in pediatric patients undergoing cardiac catheterization. They found that there was decrease in mean arterial pressure in Propofol group. This can be explained by the fact that Ketamine provides better cardiovascular stability and causes increase in heart rate and arterial blood pressure through peripheral and central mechanisms. Studies conducted by Zenup Tosun *et al*(2007) [8], Thomas MC *et al*(2011) [9], Khutia *et al* (2012) [10] also showed that the ketofol combination provided better haemodynamic stability and concluded that mean arterial pressure is better preserved when Propofol is combined with low-dose Ketamine,

It was observed that at 5 min interval after induction mean heart rate in Group 1 was 96.7±3.21 and was 93.1±14.6 in Group 2, which was statistically significant. After this interval no statistically significant difference

was found between the two groups. Bradycardia, which was managed by i.v atropine 0.01mg/kg, was found in 6 patients (20%) in Group 2 while none in Group 1. Our findings were similar to study conducted by Zenup Tosun *et al* (2007) [8]. In their study they found that heart rate after induction was significantly lower in Propofol-Fentanyl group than Propofol Ketamine group (P <0.01). This bradycardia may be due to combined effect of Propofol and Fentanyl. Propofol depresses the baroreceptor reflex control of heart rate while Fentanyl may stimulate the vagal nuclei in medulla leading to decrease in heart rate. Tomatir *et al* (2004) [11] conducted a study in 43 children aged nine days to seven years who required sedation for elective magnetic resonance imaging were randomly assigned to receive Propofol monotherapy or a combination of Ketamine and Propofol.

They observed that blood pressure and heart rate decreased significantly in the Propofol group, while there was less decrease in heart rate in Propofol Ketamine group which was statistically not significant. However, in a study conducted by Soliman R *et al* (2017) [12] found that there was no significant difference in heart rate in between Propofol and Ketofol group for sedation of pediatric patients who were scheduled for elective pulmonary valve implantation in a catheterization laboratory.

Mean SpO_2 (%) and respiratory rates were almost same between both the groups. There was statistically no significant difference in Spo2 and respiratory rate between two groups (p>0.05). Our findings were similar to findings of Zenup Tosun *et al* (2008) [13]. Erden IA *et al* (2009) [14] conducted a study to compare the frequency of adverse effects, sedation level, recovery characteristics in pediatric patients receiving intravenous Propofol-Fentanyl combination with or without Ketamine for interventional radiology procedures. In their study apnea was not observed in any of the groups. Thus they concluded that addition of low dose Ketamine to Propofol-Fentanyl combination reduces the risk of desaturation. Similar to this study, we did not observe apnoea in any patient of either group in our study. It was observed that mean RSS was almost same till 5 min after induction in both the groups. After 10 min significant difference was found between two groups, deeper level of sedation was observed in Group 1. Thus there was a statistically significant difference in RSS between two groups (p value < 0.05). In our study we used continuous infusion, so as to achieve a steady state level of sedation. For this we used Ramsay Sedation Score which is easy to use and understand and can be used in any setup. By using the desirable aspects of each drug while offsetting the adverse effects of each other, the Propofol-Ketamine combination resulted in sedation which was higher and better maintained than Propofol-Fentanyl combination.

Our study findings were similar to those of Akin A *et al* (2005) [15] In their study, they also used Ramsay sedation score and compared Propofol with Propofol-Ketamine combination for sedation in children undergoing auditory brainstem response (ABR) testing and concluded that Propofol-Ketamine provided better sedation. In contrast to our study Zenup Tosen *et al* (2008) [13] found no significant difference in sedation scores, but found that Propofol-Ketamine combination was better than Propofol-Fentanyl combination because of less restlessness in patients.

In our study we found hypotension in 5 (16.6%) patients in Group 1 and in 12 (40%) in Group 2 which was managed by iv fluid bolus or vasoconstrictors. Bradycardia was found in 6 (20%) patients in Group 2 and none in Group 1. Emergence reaction occurred in 6 (20%) patients in Group 1 and none in Group 2 and was managed by iv Midazolam 0.5mg/kg. PONV was observed

in 4(13.3%) in Group 1 and 2 (6.6%) in Group 2 and was managed by iv Ondansetron 0.1mg/kg. Although the incidence of PONV and emergence reaction in Group 1 is higher than Group 2 but the incidence rate is less than the usual when seen with Ketamine alone. This can be explained by the fact that the sedative and antiemetic properties of Propofol counteracted the effects of Ketamine. Studies similar to our findings A. Shah et al (2011) [16] and William EV *et al* (2006) [17], Kim S, Hahn *et al* (2019) [18] also observed that the incidence of hypotension, bradycardia, respiratory depression, were less in Propofol-Ketamine group. In contrast Gad EL-Rab NA *et al* (2019) [17] found no significant difference in side effects between propofol-ketamine and propofol-fentanyl groups for sedation during paediatric diagnostic UGI endoscopy.

Mean recovery time in Group 1 was 10.06±1.55 while in Group 2 was 8.36±1.66. It Thus there was a statistically significant difference in recovery time between two groups. Our findings were similar to study conducted by Sandip A Godambe *et al* July (2003) [19] they compared two regimes Propofol/Fentanyl (P/F) and Ketamine/Midazolam (K/M), for short orthopedic emergency surgeries in paediatric patients aged 3-18 years requiring procedural sedation.

They observed that recovery times were significantly less in the P/F group than in the K/M group. In contrast Gary Andolfotto *et al* (2010) [20] found shorter recovery times with intravenous (iv) ketofol (mixed 1:1 Ketamine-Propofol) for procedural sedation and analgesia (PSA) in children. This disparity of findings could be due to difference in dosages of drugs administered and procedural characteristics

Conclusion

Thus, we conclude that Ketamine-Propofol combination provides safe and effective sedation, profound analgesia, lesser degree of hypotension, minimal respiratory depression and least adverse effects compared to Fentanyl-Propofol combination. Ketamine-Propofol infusion was found to be superior and safer regimen than Fentanyl-Propofol infusion in terms of hemodynamic stability, sedation and analgesia in paediatric patients undergoing short surgical procedures.

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