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Propofol or propofol ketamine a better combination in Ambulatory Anesthesia: A comparative study

Dr. Sanjul Dandona[1], Dr. Surinder Singh[2*]
[1] Assistant Professor, Department of Anaesthesiology, VCSGGMS & RI Srinagar Garhwal, Uttrakhand, India
[2] Associate Professor, Department of Anaesthesiology, VCSGGMS & RI Srinagar Garhwal, Uttrakhand, India

Abstract
Present study was conducted to compare the clinical efficacy of propofol alone with propofol ketamine combination during ambulatory anesthesia. Hospital Based study wich is a randomized double blinded study was conducted in 80 patients in the department of anaesthesiology VCSGGMS & Research Institute, Garhwal, over a period of about 2 yrs. Patients belonging to ASA I & II, aged between 20-40 yrs, 40 in each group was taken. Group P: Propofol alone Group PK: Propofol ketamine combination. Induction doses, pulse rate, oxygen saturation, systolic, diastolic blood pressure, mean arterial pressure and complication if any were recorded. The parameter were subjected to T test analysis and found statistically significant difference in induction dose, systolic, diastolic, mean arterial pressure & complication.

Keywords: propofol, ketamine, total intravenous anaesthesia, ambulatory (TIVA)

Introduction

1. Use of anesthesia with the aim to admit and discharge the patients on the present day of the surgical procedure is called as ambulatory anesthesia.
2. Total intravenous anesthesia is a technique in which induction and maintance of anesthesia is achieved with intravenous drugs alone, thus avoiding both volatile agents and nitrous oxide.
3. Propofol (2, 6, di-isopropyl phenol) is the most recent intravenous anaesthetic to be introduced into clinical practice and is being widely used due to its hemodynamic property. Propofol is a non-opioid, non-barbiturate, sedative hypnotic agent. It possesses anti emetic effect & reliably produces sedation. Because of its clear headed recovery nature it is preferred in ambulatory surgeries. Side effects include dose related cardiovascular & respiratory depression, bradycardia and hypotension. It also lacks analgesic property.

Ketamine is phencyclidine derivative & known to produce analgesia & amnesia. It causes minimal respiratory depression and does not cause myocardial depression. However ketamine when used as a sole agent for procedural sedation & analgesia results in occurrence of emergence reactions, which are associated with dreaming, delirium and illusions. In few cases laryngospasm and airway obstruction has also been noted.
This study is designed to compare propofol alone with propofol and ketamine for TIVA in ambulatory anesthesia.

Material and Methods

The present study was carried out in the department of anaesthesiology at VCSSG Govt medical College & RI (Garhwal), after obtaining institutional ethical committee aproval and patients written informed consent, the study was conducted in 80 patients, aged 20 to 40 yrs of ASA grade I and ASA grade II, scheduled for ambulatory anesthesia i.e. incision and drainage of abscesses, closed reduction of fracture upperlimb. The patients were randomly allocated in two different groups (40 of each) i.e. propofol alone (Group P) and combination of propofol & ketamine (Group PK) and following things are to be recorded i.e

1. Haemodynamics, intra operatively.
2. Induction requiremts, of propofol and ketamine.
3. Time of recovery from induction.
4. Incidence of post-operative Complications.
5. Duration of pain relief post operatively.

Patients with ASA grade III, IV & V and patients below 20 yrs of age and above 40 yrs of age, unwilling Pt, history of allergy to drugs were excluded from the study. Mode of selection was randomized double blind.
18 G Cannula, Drugs, Disposable Plastic Syringes and …..(SpO2, PR. NIBP) anesthesia machine, Resuscitation Equipment's (stand by).
All pt were kept fasting for at least 6hrs prior to anesthesia. Preoperative base line heart rate, BP, respiratory rate SpO2 were recorded.

Intra Operative Period: After securing 18 G cannula and connecting to NIBP, pulse oximeter and ECG monitor, patients were premeditated 15 to 20 mint prior to induction with

1. Injection Glycopyrulate 0.2mg.
2. Injection ondansetron 4mg.
3. Injection fentanyl 1microgram per kg.
4. Injection midazolam 1mg.

The anaesthesia machine was kept ready along with oxygen delivery system, emergency resuscitation equipment's and emergency drugs.
In a double blind manner pt. were randomly assigned to one of

the two group's i.e.

- Group P: 40 pt. received propofol slowly till the point of induction.
- Group PK: 40 pt. received ketamine 0.5mg per kg IV slowly followed by propofol IV till the point of induction.

Baseline Blood Pressure, Pulse rate, respiratory rate, SpO2 were recorded.

Then the anaesthesia was maintained with propofol bolus 10mg IV in propofol group, Propofol ketamine bolus 10+10mg IV in propofol-ketamine group based on requirements-namely-spontaneous moments, tachycardia, high blood pressure, increase in respiratory rate, appearance of tears. Spontaneous respiration was maintained with 100% O2 with mask and bain's circuit.

Blood Pressure, ECG Changes, Respiratory rate, basal pulse rate and saturation were noted followed by every 5 minutes recording till the end of the procedure. Post operatively duration of pain relief was also noted.

For nausea and vomiting inj ondansetron 100-150 microgram per kg IV was given. The time for first analgesic demand was noted. The regular analgesics were administered for the remaining 24hrs for pain relief to the pt.

Hypertension defined as >140/90 mm of hg

Hypotension defined as < 90/50 mm of hg

Hypoventilation defined as respiratory rate <8/minute

Desaturation defined as SPO2 <93%

All the parameters were monitored very keenly.

Statistical analysis

The Student T-Test was used to assess the statistical significance of paired date a p value of <0.05 was considered significant.

Observations and Results

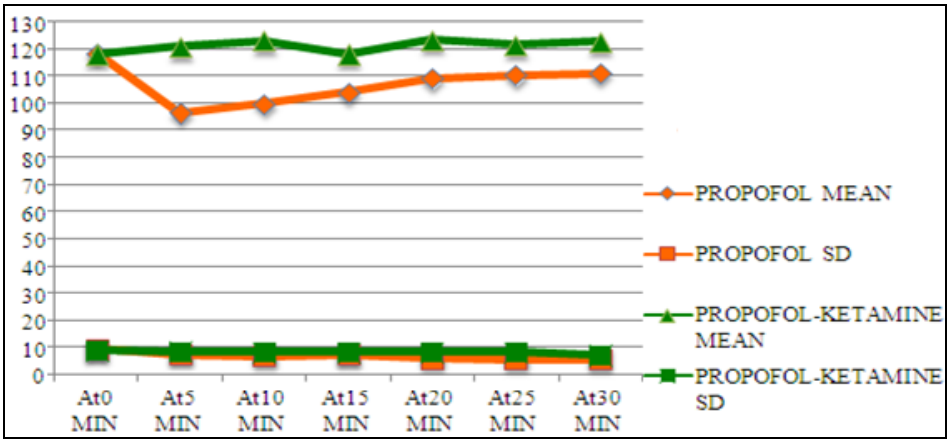
The results are as follows:

Demographic profiles of the patients scheduled for study were comparable.

Table 1: Intergroup comparision of changes in systolic blood pressure

Mean Systolic BP	Propofol		Propofol-Ketamine		T stat	P - Value	Inference
	Mean	SD	Mean	SD			
At0 MIN	118.4	9.36	117.9	8.77	0.22	>0.05	NS
At5 MIN	96.3	7.35	120.6	8.28	-13.89	<0.001	HS
At10 MIN	99.7	6.68	122.9	8.14	-13.96	<0.001	HS
At15 MIN	103.8	7.03	117.9	7.99	-8.43	<0.001	HS
At20 MIN	108.9	5.64	123.3	7.93	-9.33	<0.001	HS
At25 MIN	110.1	5.35	121.4	7.95	-7.46	<0.001	HS
At30 MIN	110.9	5.45	122.6	6.99	-8.31	<0.001	HS

NS-Nothing significant, HS-Highly significant



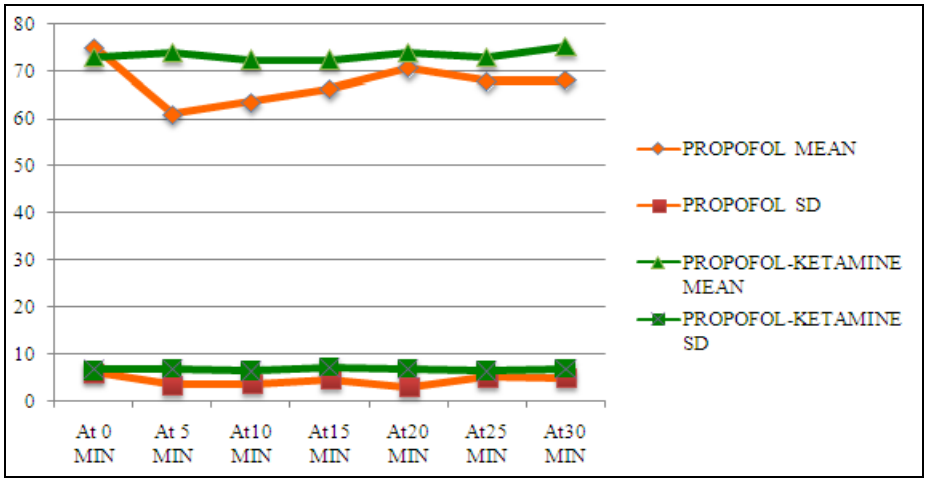
SD-Standard Deviation

Fig 1: Intergroup comparision of changes in systolic blood pressure

Table 2: Intergroup comparision of changes in Diastolic blood pressure

Mean Diastolic BP	Propofol		Propofol-Ketamine		T stat	P - Value	Inference
	Mean	SD	Mean	SD			
At 0 MIN	75.1	6.14	72.9	6.67	1.53	>0.05	NS
At 5 MIN	60.9	3.54	74.0	6.84	-10.76	<0.001	HS
At10 MIN	63.4	3.77	72.4	6.50	-7.61	<0.001	HS
At15 MIN	66.3	4.68	72.5	7.19	-4.53	<0.001	HS
At20 MIN	70.6	3.08	73.9	6.84	-2.74	<0.05	HS
At25 MIN	67.9	5.07	72.9	6.39	-3.84	<0.001	HS
At30 MIN	68.1	4.93	75.3	6.83	-5.44	<0.001	HS

NS-Nothing significant, HS-Highly significant



SD-Standard Deviation

Fig 2: Intergroup comparision of changes in Diastolic blood pressure

Table 3: Intergroup comparision of changes in pulse rate

Mean PR	Propofol		Propofol-Ketamine		T stat	P Value	Inference
	Mean	SD	Mean	SD			
AT0 MIN	79.3	5.86	77.6	4.78	1.42	>0.05	NS
AT5 MIN	72.9	5.24	77.6	4.99	-4.06	<0.001	HS
AT10MIN	72.2	4.87	77.5	5.10	-4.71	<0.001	HS
AT15MIN	72.3	5.42	78.9	5.73	-5.33	<0.001	HS
AT20MIN	72.3	5.16	77.4	5.29	-4.37	<0.001	HS
AT25MIN	72.7	4.89	80.0	6.04	-5.98	<0.001	HS
AT30MIN	73.1	4.92	78.6	5.49	-4.68	<0.001	HS

NS-Nothing significant, HS-Highly significant

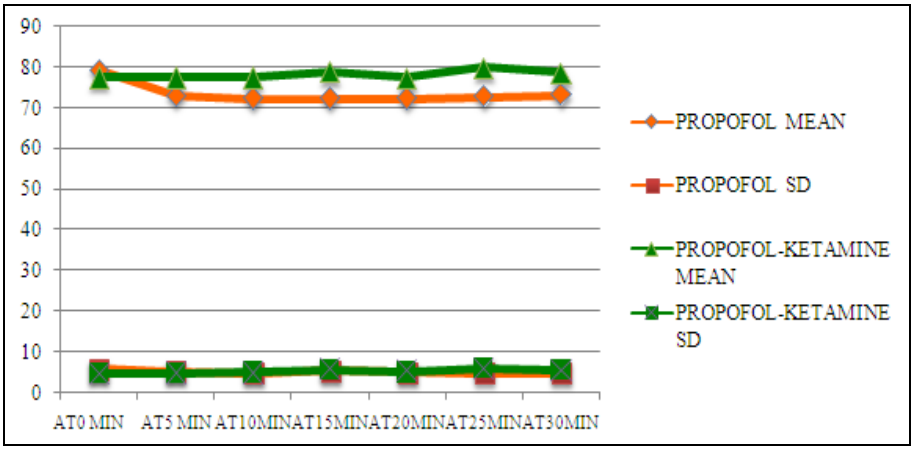
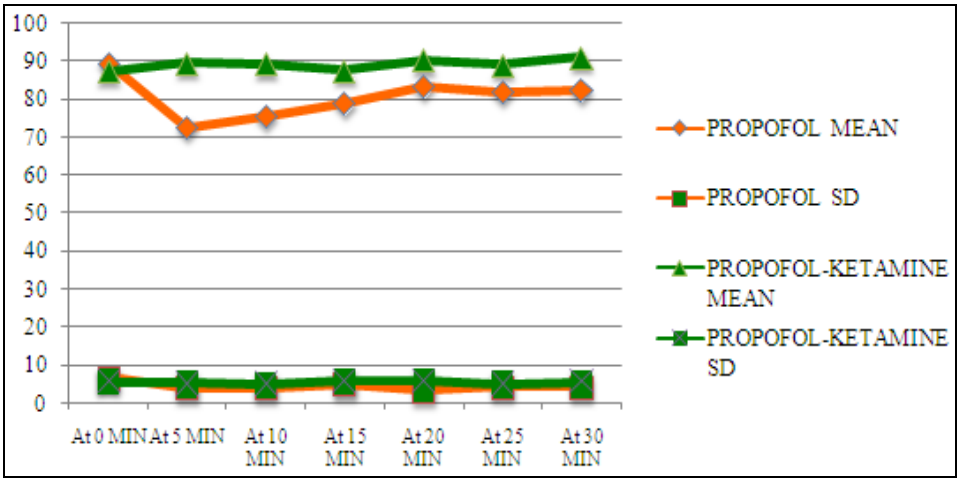


Fig 3: Intergroup comparision of changes in pulse rate

Table 4: Intergroup comparision of changes in Mean arterial pressure

Mean Arterial Presure	Propofol		Propofol-ketamine		T stat	P - Value	Inference
	Mean	SD	Mean	SD			
At 0 MIN	89.5	6.94	87.3	5.74	1.48	>0.05	NS
At 5 MIN	72.6	4.09	89.5	5.39	-15.73	<0.001	S
At 10 MIN	75.4	4.14	89.2	5.17	-13.14	<0.001	S
At 15 MIN	78.8	4.99	87.6	6.03	-7.11	<0.001	S
At 20 MIN	83.3	3.45	90.3	5.86	-6.46	<0.001	S
At 25 MIN	81.9	4.46	89.1	5.33	-6.48	<0.001	S
At 30 MIN	82.3	4.34	91.1	5.67	-7.73	<0.001	S

NS-Nothing significant, HS-Highly significant, S-Significant



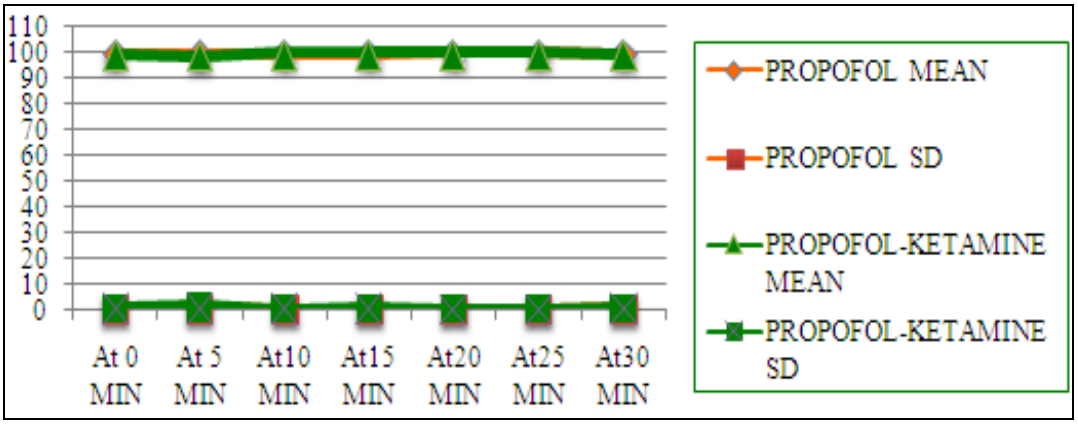
SD-Standard Deviation

Fig 4: Intergroup comparision of changes in Mean arterial pressure

Table 5: Intergroup comparision of changes in mean oxygen saturation

Mean oxygen saturation	Propofol		Propofol-Ketamine		T stat	P - Value	Inference
	Mean	SD	Mean	SD			
At 0 MIN	99.8	0.67	99.5	0.96	1.22	>0.05	NS
At 5 MIN	99.6	0.81	98.6	1.52	3.68	<0.001	HS
At10 MIN	99.8	0.61	99.8	0.67	0.35	>0.05	NS
At15 MIN	99.8	0.61	99.8	0.81	0.35	>0.05	NS
At20 MIN	99.9	0.53	99.8	0.61	0.39	>0.05	NS
At25 MIN	100.0	0.53	99.9	0.53	0.28	>0.05	NS
At30 MIN	99.8	0.67	99.5	0.90	1.69	>0.05	NS

NS-Nothing significant, HS-Highly significant



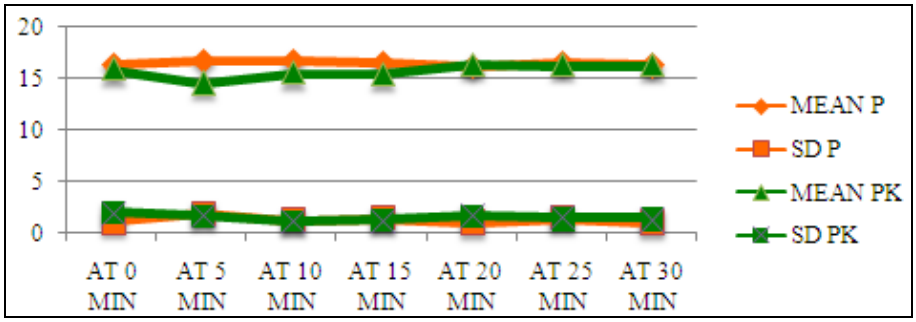
SD-Standard Deviation

Fig 5: Intergroup comparision of changes in mean oxygen saturation

Table 6: Intergroup comparision of changes in mean respiratory rate

Mean Respiratory Rate	Propofol		Propofol-Ketamine		T stat	P - Value	Inference
	Mean	SD	Mean	SD			
At 0 MIN	16.3	1.19	15.8	2.07	1.35	>0.05	NS
At 5 MIN	16.75	1.96	14.5	1.74	5.43	<0.001	HS
At 10 MIN	16.7	1.32	15.45	1.19	4.43	<0.001	HS
At 15 MIN	16.45	1.47	15.35	1.31	3.54	<0.001	HS
At 20 MIN	16.15	1.05	16.35	1.78	-0.77	>0.05	NS
At 25 MIN	16.5	1.47	16.25	1.58	0.87	>0.05	NS
At 30 MIN	16.3	1.07	16.2	1.47	0.43	>0.05	NS

NS-Nothing significant, HS-Highly significant



SD-Standard Deviation

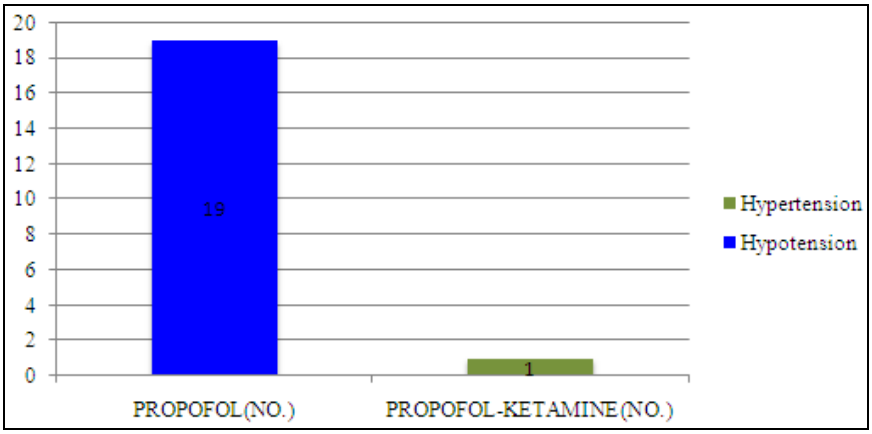
Fig 6: Intergroup comparision of changes in mean respiratory rate

Table 7: Induction dose requirements of propofol in both groups

	Induction dose (Mean+/-SD)mg/kg	P value
Propofol group	2.02+/-0.16	<0.001
Propofol-Ketamine group	1.62+/-0.1	

Table 8: Time to recover from induction doses in study groups NS-Nothing significant, HS-Highly significant NS-Nothing significant, HS-Highly significant

	Mean		P Value	Inference
	Propofol (MIN)	Propofol-Ketamine(MIN)		
Time of recovery from induction dose	2.63	9.80	<0.001	HS



(NO. – Number)

Fig 7: Intergroup comparision of sideeffects/complications

Table 9: Duration of pain relief postoperatively/time taken for first analgesic demand

Propofol	Propofol-Ketamine	
Time for first analgesic demand (MIN)	8.6 +/- 1.89	48.5 +/- 7.61

Discussion

The total intravenous anaesthesia has been a subject of interest for all anaesthesiologists, as this is the best route to avoid operation theatre pollution.

With the invention of continous infusion system TIVA gained popularity but even today, we are still without any one IV drugs that can alone provide all the requirements of anaesthesia (i.e unconsciousness, analgesia and muscle relaxation). Hence there is need to administer several different agent to produce the desired results.

Ketamine when used in subanaesthetic dose reduces the dose of propofol required for induction. This is known as co-induction. It provides haemodynamic stability.

1- IN 2001 kaushik saha *et al* too found a statistically significant decrease in the induction dose of propofol in combination with ketamine, in comparision to fentanyl. In our study also, induction dose of propofol was decreased in propofol-ketamine combination group.

2-In 1981 study done by Briggs and co-workers using different doses of propofol (1-3mg/kg) as a main agent for short surgical procedures. They found that with the 1.75 mg/kg not all patients were anaesthetized and 2 mg/kg was a satisfactory induction dose. Recovery was rapid with almost all patients and there was absence of emetic sequel.

Similar to the study of Briggs and co-workers, our study was also found the mean induction dose requirement of propofol in propofol alone group was 2.02+/0.16 mg/kg. And in propofol-ketamine group mean induction dose of propofol was 1.6+/-0.10 mg/kg. which was statistically significant.

3-The study done by Shiba goel MD, Neerja Bhardwaj MD in

2008 to know the efficancy of ketamine (pk) and midazolam (PM) as co-induction agent with propofol (P) for laryngeal mask insertion in children. In group P, systolic blood pressure showed a significantly greater decrease compared to group PK and group PM (P<0.005).

Only 5% of patients in groups PK and PM showed >20% fall in SBP compared to 89% in group P(P<0.005). More children in groups PK and PM had acceptable conditions for LM insertion compared to group P(P<0.05). The time to achieve Steward Score of 6 was longer in groups PK and PM compared to group P(<0.005). In children, the combination of propofol with ketamine or midazolam produces stable hemodynamics and improved LM insertion conditions but is associated with delayed recovery.

Hence the present study was undertaken to study the effectivencess of ketamine as co-induction agent with propofol in comparision to propofol alone.

4-In 2014 a study was done by Fernando Martinez- Taboada and Elizabeth, A leece to compare anaesthetic induction in 70 healthy dogs using propofol or ketofol (apropofol-ketamine mixture), following premedication. either propofol (10mg/ml) of ketofol (9mg propofol and 9mg ketamine/ml) was titrated intravenously until laryngoscopy and tracheal intubation were possible. Induction mixture volume (mean±SD) was lower for ketofol (0.2±0.1 ml kg) than propofol (0.4±0.1 ml/kg)(p<0.001). PR increased following ketofol (by 35±20 beats minute) but not consistenly following propofol (4±16 beats minute)(p<0.001). Ketofol administration was associated with a higher mean arterial blood pressure (MAP) (82±10 mmhg) than propofol (77±11)(p=0.05). Ketofol use resulted in a greater decrease in FR-1 (median range): Ketofol-32 (-158 to 0) propofol -24(-187 to 2) breaths minute (p<0.001) sedation was similar between groups. Tracheal intubation and induction qualities were better with ketofol than propofol (p=0.04 and 0.02 respectively).

5-In 2010 a study done by Fernando SF Cruz Adriano B Carregaro Alceu G Raiser, Marina Zimmerman, Rafael Lukarsewski and Renata PB Steffen to evaluate TIVA with propofol (P) alone or in combination with ketamine (PK) in rabbits undergoing surgery found that ketamine potentiates propofol-induced anesthesia in rabbits, providing better maintenance of heart rate.

6-In 2008 a Study done by M. Koch, D. De Backer, J.L. Vincent, L. Barvais, D. Hennart and D. Schmartz to know the effects of propofol on human microcirculation found that the 15 pt had a mean (range) age of 35(25-41) yr. During the assessment of the microcirculation, the mean calculated propofol effect-site concentration was 6.5 micrograms. / Ml (range 4.5-10 micrograms/ml). There were no significant changes in heart rate or SpO2, but body temperature decreased during anesthesia and the arterial pressure decreased at the end of the intervention.

7-In 1991 a study was done by Guit and co-workers (A comparision of combination of propofol-fentanyl and propofol with ketamine in 18 patients who underwent non-cardiac surgery) to who concluded that propofol ketamine combination resulted in hemodynamically stable anaesthesia without the need for additional analgesics. Postoperative behavior was normal in all patients and none of the patients reported dreaming during or after operation. Propofol seems to be effective in eliminating side effects of a subanaesthetic dose of ketamine in humans.

Similar to the above studies our study also had decrease in mean heart rate, mean systolic blood pressure, mean diastolic pressure, mean arterial pressure in propofol group when compared to propofol ketamine combination group. i.e.

- Mean basal systolic blood pressure of propofol alone group was 118.4+/9.36 and in propofol-ketamine group was 117.9+/-8.77 which were statistically comparable.
- Decrease in mean systolic blood pressure was seen in propofol alone group, where maximum fall was noted at 5 minutes after induction (96.3+/-7.35) which was highly significant when compared to propofol-ketamine combination group throughout 30 minutes of observation.
- Similar fall of mean diastolic blood pressure was observed in propofol alone group from basal mean diastolic blood pressure (75.1+/6.14) maximum drop was observed at 5 minutes after induction (60.9+/-3.54) statistically significant difference was present between two groups throughout the 30 minutes observation.
- Similar decrease in mean arterial pressure was noted in propofol alone group when compared to propofol-ketamine group, which was statistically significant.

There was a significant decrease in mean pulse rate statistically after propofol induction in propofol alone group after successive intervale i.e. 5,10,15,20,25,30 minutes was 72.9+/-5.24, 72.2+/-4.87, 72.3+/-5.42, 72.3+/-5.16, 72.7+/-4.89, 73.1+/-4.92 respectively, mean basal pulse rate of propofol-ketamine group was 77.6+/-1.42, mean pulse rate at 5,10,15,20,25,30 intervals was 77.6+/-4.78, 77.5+/-5.10, 78.9+/-5.73, 77.4+/-5.29, 80.0+/-6.04, 78.6+/-5.49 respectively.

In 2014 Fernando Martinez Taboada and Elizabeth a Leece Conducted a study to compare anaesthetic induction in 70 healthy dogs using propofol or ketofol (apropofol-ketamine mixture), following premedication, either propofol (10mg/ml) or ketofol (9mg propofol and 9mg ketamine/ml) was titrated intravenously until laryngoscopy and tracheal intubation were possible. Ketofol use resulted in a greater decrease in respiratory rate (median range. Ketofol-32(-158 to 0) propofol -24(-187 to 2) breaths minute) (p<0.001). Sedation was similar between groups.

8-In 2001 Rosendo Mortero *et al* from the University of loursvilla, KY who were posted for monitored anaesthesia care, conducted a study in 40 patients to see the effects of a small dose of ketamine on propofol in terms of sedation, respiration, post-operative moodperception, cognition and pain. They concluded that co-administration of small dose ketamine attenuates propofol induced hypoventilation, produces positive mood effects without perceptual changes after surgery, and May provided earlier recovery of cognition.

Similar to the above study, out study also showed reduction in respiratory rate in propofol-ketamine combination group uat 5,10,15 minutes when compared to propofol alone group which was statistically significant for some period (till 15 minutes), after that there was no significant difference between two group. But there was no hypoventilation or apnea.

9-In 1970 a study was conducted by Knox *et al* to see the duration of anaesthesia with ketamine induction lasted for 13.2+/-1.25 minutes.
10-In 1983 a study was conducted by Diwale *et al* showed that duration of anaesthesia with ketamine induction lasted for 5-17 minutes.
11-Schuttler and Coworkers did optimal dosage strategies in total intravenous anaesthesia using propofol-ketamine. 20 patients were scheduled for lower abdominal interventions. The patients were divided into two groups, anaesthesia was induced and maintained by a simole administration regimen and the second group received propofol and ketamine by microprocessor controlled infusion pumps and the concluded that TIVA with propofol and ketamine prove to be satisfactory from clinical point to view. The major side effect of propofol and ketamine disturbances were absent and respiratory function was adequate at the end of surgery.
A study was conducted by M.Koch. D. De Backer. J.L. Vincent I. Barvais, D.Hennart and D. Schmartz in 2008 to know the effects of propofol on human microcirculation found that the 15 patients had a mean (range) age of 35(25-41) yr. During the assessment of the microcirculation, the mean calculated propofol effect-site concentration was 6.5 micrograms/ml (range 4.5-10 micrograms/ml). There were no significant changes in heart rate or SpO2, but body temperature decreased during anaesthesia and the arterial pressure decreased at the end of the intervention.
Hypertension was noted in 1 patient in propofol-ketamine group.
12-In 2013 study was conducted by Sherry N. Rizk, Enas M Samir regarding use of ketofol to control emergence agitation in children undergoing adenotonsillectomy in 90 children. They were randomly assigned to receive 10ml of normal saline (control Group C) or, 1 mg/kg propofol in 10ml saline (group P) or ketofol as 1mg/kg propofol and 0.25mg/kg ketamine in 10 ml saline (group K) 10 min before the end of surgery. In PACU, sedation, behavior, pain and severity of emergence delirium were assessed. Emergence delirium was significantly more frequent in the control group ($p<0.001$), but comparable in ketofol and propofol groups. Ketofol provides a promising new option for controlling emergence agitation with adequate postoperative sedative and analgesic effect, good recovery criteria and hemodynamic stability compared to propofol and control groups in children undergoing adenoidectomy or adenotonsillectomy.
Similar to above study, emergence delirium was not observed in ketofol group none of the patients experienced emergence delirium in our study.
In 2001 study was conducted by Kaushik Sha*et al* to compare fentanyl and ketamine each with propofol for minor gynecological procedures and they found excellent analgesia with ketamine0.5 mg/kg.
Duration of pain relief was lesser in propofol alone group when compared to propofol-ketamine group. Propofol group required analgesics earlier than propofol-ketamine postoperatively 33.33% in propofol group required analgesia in 0-1 hour post operatively, whereas only 11% required analgesic dose in first postoperative hour propofol group needed higher analgesic requirements.
Mean time taken for first analgesic demand in propofol group was 8.6+/-1.89, where as in propofol-ketamine group 48.5+/-7.61 minutes.

Conclusion

Our study concluded that propofol ketamine combination (PK) as compared to propofol (P) provides better haemodynamic stability as there is less induction requirements of propofol with less side effects and also the duration of pain relief post operatively was longer. Time to recover from induction dose was prolonged in propofol ketamine group.

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