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EFFECT OF TWO DRUG COMBINATIONS PROPOFOL-KETAMINE AND PROPOFOL-FENTANYL ON HEMODYNAMIC PARAMETERS AND RECOVERY FROM ANAESTHESIA IN TIVA-A COMPARATIVE STUDY.

Anaesthesiology

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ABSTRACT

Introduction- Total Intravenous anaesthesia(TIVA) is widely used procedure. We compared the effect of propofol-ketamine combination with propofol-fentanyl combination on hemodynamic parameters and recovery of patients undergoing TIVA. **Aims and Objective-** To compare the effect of combination of propofol and ketamine and combination of propofol and fentanyl for TIVA, on hemodynamic parameters and recovery from anaesthesia. **Material and Method-** Patients aged 20- to 60-year-old, ASA-PS I and II, undergoing elective surgeries were selected for the study and were divided into two groups (1 and 2) of 90 each. TIVA was administered in the two groups as- Group-1 Induction- Propofol 1.0mg/kg+Ketamine 1.0mg/kg, iv boluses. Maintenance- Propofol 2.0 mg/kg/h and Ketamine 2.0 mg/kg/h, iv infusion. Group-2 Induction- Propofol 1.0mg/kg+Fentanyl 2.0µg/kg, iv boluses. Maintenance- Propofol 2.0mg/kg/h and Ketamine 2.0µg/kg/h, iv infusion. All the patients were mechanically ventilated with 100% oxygen. Neuromuscular blockade achieved with Vecuronium-bromide. Vital-parameters were recorded at regular intervals and DJ Steward recovery score was calculated. **Result-** Following induction, heart rate (HR) increased in Group-1 and decreased in Group-2 and mean blood pressure (systolic and diastolic) increased in Group-1 while it decreased in Group-2. HR and blood pressure(BP) returned towards baseline during maintenance in both the groups. HR and BP increased in both the groups following extubation but gradually returned to baseline. Group-1 scored higher on ventilation, whereas Group-2 scored higher on wakefulness and movement. Though the difference became insignificant post 10 minutes. **Summary-** Both propofol-ketamine and propofol-fentanyl combinations can be utilized in TIVA for short elective procedures because they offer effective surgical anaesthesia with little strain on hemodynamic parameters, which helps to preserve stability and speed up recovery.

KEYWORDS

TIVA, Propofol, Ketamine, Fentanyl.

INTRODUCTION

In TIVA, numerous medications have been tried. Since no one medication can satisfy all the requirements of the ideal intravenous agent, a variety of medications are combined to achieve balanced anaesthesia in TIVA, which includes amnesia, hypnosis, and analgesia (Bajwa et al., 2010). In subhypnotic doses, propofol, which is primarily a hypnotic, causes sedation and amnesia. It is suitable for short surgical procedures because, as a result of its high hepatic clearance, it swiftly leaves the blood. This leads to a fast return of cognitive and psychomotor functioning with a very low incidence of post-operative nausea and vomiting (PONV). Since propofol lacks analgesic qualities, TIVA should incorporate additional analgesic medications. Modern analgesics have taken the place of older ones like morphine and pethidine, such as fentanyl, sufentanil, alfentanil, and remifentanil (Peng & Sandler, 1999).

Aside from propofol, the most popular drugs for TIVA include remifentanil, alfentanil, sufentanil, ketamine, midazolam, and dexmedetomidine. These may be administered as boluses or as continuous infusions. The medications can be delivered using a manual infusion method or a Target Controlled Infusion. Daycare procedures can also be performed with TIVA (MANI & MORTON, 2010; ROBERTS et al., 1988).

Both propofol and ketamine as well as propofol and fentanyl may be utilised in TIVA. These can be administered continuously or in the form of numerous bolus incremental doses. Ketamine has received increased attention as a TIVA analgesic when used in subanesthetic doses (Bajwa et al., 2010; Slogoff & Allen, n.d.). Both ketamine and fentanyl are strong analgesics. Fentanyl is currently the most popular opioid used in clinical anaesthesia, while ketamine has a high margin of safety (Tiwari et al., 2018).

This study has been taken up to compare common drugs used in TIVA in order to find out a better one. We have compared the effect of combination of propofol and ketamine with propofol and fentanyl on hemodynamic parameters and assessed the recovery from anaesthesia using the Steward Recovery scoring system (Steward, 1975).

AIMS AND OBJECTIVE

To compare the effect of combination of propofol and ketamine and combination of propofol and fentanyl for TIVA, on hemodynamic parameters- Heart Rate, Systolic Blood Pressure, Diastolic Blood Pressure, during induction, maintenance and recovery from anaesthesia.

To compare the recovery from TIVA administered with propofol and ketamine with the recovery from TIVA with propofol and fentanyl.

METHODS

Place Of Study: Department of Anaesthesiology, Assam Medical College & Hospital, Dibrugarh, Assam, India.
Duration Of Study: One Year (June 2021 to May 2022)
Type Of Study: Hospital Based Observational Study
Chi Square and Student's t tests were used to analyse the data. A p-value of 0.05 or less was regarded as statistically significant, whereas a value of 0.05 or greater was regarded as non-significant.
Sample Size: By considering 95% confidence interval of 80% power and findings of the study by Bajwa SJ et al (Bajwa et al., 2010)[1] as reference, the sample size for the present study was calculated and rounded off to be 90 in each group.

Inclusion Criteria For Patients

- Age of the patient were between 20 – 60 years
- Patients who had Body Mass Index (BMI) < 30 were selected.
- Duration of surgery less than 80 minutes.
- Patients belonged to ASA class I or II.
- Patients with normal hematological and biochemical parameters.
- Written informed consent was obtained from each eligible patient, who agreed to participate in the study.

Exclusion Criteria For Patients

- Patients who refused to participate.
- Patients with hypersensitivity to the drugs used.
- Patients with history of malignant hyperthermia, previously

diagnosed renal disease, liver disease, any electrolyte abnormalities and/or neurological diseases.
- Patients on Monoamine oxidase inhibitors.
- Patients with difficult airway.
- Pregnant and lactating mothers.
- Any emergency surgery case.

Patients who were planned to undergo elective surgeries under general anaesthesia, at Assam Medical College and Hospital, were divided into two groups of 90 each (total- 180 patients). Informed written consents were taken from the patients who willfully agreed to participate.

Subjects were divided into two equal groups, Groups-1 and 2. For the induction and maintenance of anaesthesia, Group-1 received the medication combination propofol-ketamine, while Group-2 received propofol-fentanyl.

Pre-operative Evaluation

The day before surgery, all patients were required to go through a thorough pre-anaesthetic evaluation in their individual wards. An extensive clinical examination was conducted after taking the patient's complete medical history, including any information on any prior operations, drug allergies, or prolonged medical treatment. Depending on the clinical profile of the patient and the proposed surgery, suitable laboratory investigations were then performed.

Anaesthetic Technique

In the operating room standard ASA monitors were connected. The baseline hemodynamic parameters were recorded. Intravenous line was secured with 18 G cannula and Ringer's lactate solution was started.

Patients were premedicated with IV Ondansetron (0.15 mg/kg) and injection glycopyrrolate (0.04 mg/kg), IV Tramadol (3 mg/kg). Injection Midazolam (0.08 mg/kg with maximum dose of 5 mg) was given IV 2 minutes before the induction of anaesthesia in both the groups. Pre-oxygenation was carried out with 100% Oxygen for 3 minutes.

Induction of anaesthesia- In Group-1, induction of anaesthesia was carried out with propofol 1.0 mg/kg body wt (weight). and ketamine 1.0 mg/kg body wt iv boluses. In Group-2 induction was carried out with propofol 1 mg/kg body wt. and fentanyl 2.0 µg/kg body wt iv boluses. Injection Succinyl choline 1.5mg/kg was used as a muscle relaxant for intubation.

Maintenance of anaesthesia- For maintenance of anaesthesia in Group-1, infusion of propofol 2.0 mg/kg/h and ketamine 2.0 mg/kg/h was used, while in Group-2, infusion of propofol 2.0 mg/kg/h and fentanyl 2.0 µg/kg/h was used. Vecuronium bromide was used as a muscle relaxant during the maintenance peiod with a dose of 0.05-0.06mg/kg body wt as bolus and intermittent top-ups of 1mg.

Heart rate, systolic blood pressure, and diastolic blood pressure were recorded at baseline, induction, intubation, then 2 and 5 minutes after intubation, then at incision, 2, 5, 15 minutes after incision and then at every 15 minutes intervals till end of anaesthesia. Data was recorded again at extubation and then at every 10 minutes intervals thereafter, till 60 minutes. Monitoring of vitals and the recording of data continued into the recovery period.

The Simplified Post-Anesthetic Recovery score by D.J. Steward (Steward, 1975) was used to measure recovery and compare it between the two groups immediately following surgery and every five minutes until the discharge requirements were satisfied.

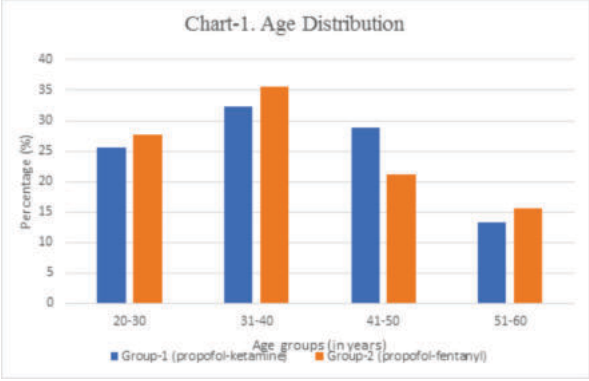
The simplified Post-Anaesthetic Recovery Score	
Awake	
Fully Awake	2
Arousable	1
Not responding	0
Ventilation	
Coughing on command or crying	2
Breathing easily	1
Airway requires attention	0
Movement	
Moving limbs purposefully	2
Non-purposeful movements	1
Not moving	0

RESULTS

Demographic Data

Table-1. Age Distribution

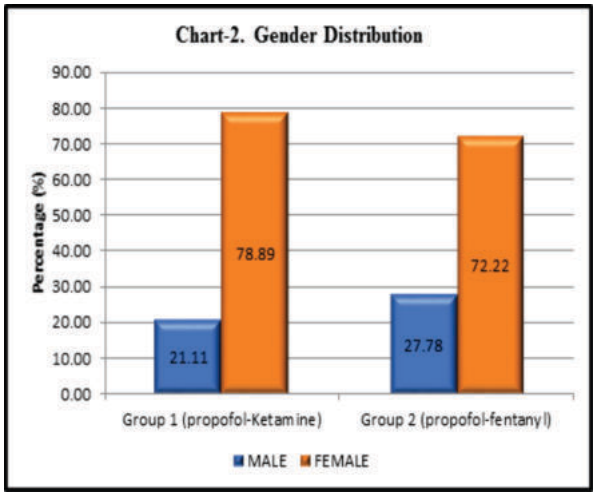
Age in Years	Group-1		Group-2	
	N	%	N	%
20-30	23	25.56	25	27.78
31-40	29	32.22	32	35.56
41-50	26	28.89	19	21.11
51-60	12	13.33	14	15.56
TOTAL	90	100	90	100
Mean S.D	38.08 ± 10.85		38.26 ± 9.96	
p-value	0.9090			
Student's t-Test				



The mean ages in both the groups were comparable. The mean age, in years, in Group-1 was 38.08 ± 10.85 years, and in Group-2 was 38.26 ± 9.96 years. p-value is 0.9090 (p-value > 0.05), statistically insignificant,

Table-2. Gender Distribution

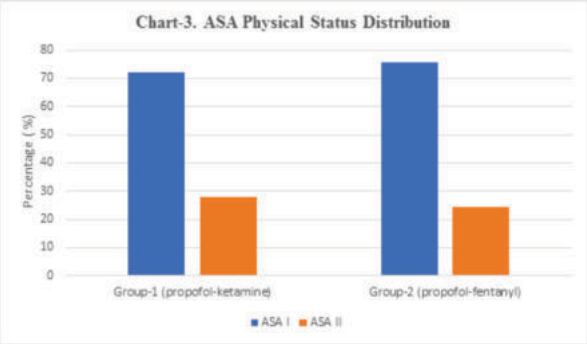
Gender	Group-1		Group-2		p-value
	N	%	N	%	
Male	19	21.11	25	27.78	0.3865
Female	71	78.89	65	72.22	
Total	90	100	90	100	
Chi-Square test					



The gender distribution in both the groups were comparable. The percentages of males and females in Group-1 was 21.11% and 78.89%, and that in Group-2 was 27.78% and 72.22%, respectively. These values were comparable and statistically insignificant (p-value > 0.05).

Table-3. ASA Physical Status Distribution

ASA status	Group-1		Group-2		p-value
	N	%	N	%	
ASA I	65	72.22	68	75.56	0.610
ASA II	25	27.79	22	24.44	
Total	90	100	90	100	
Chi-Square test					

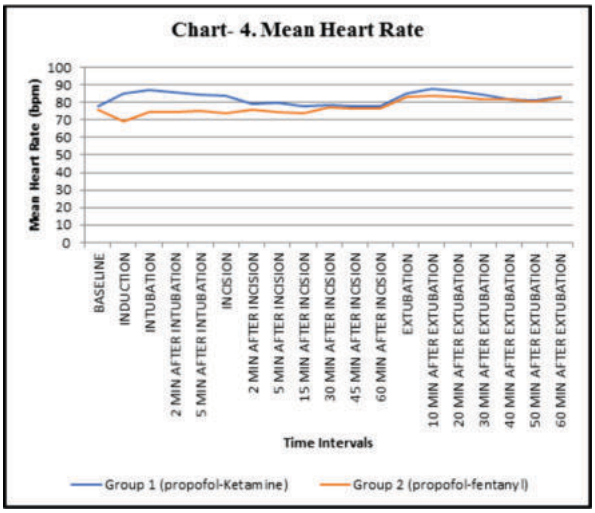


ASA PS I and ASA PS II percentages in Group-1 was 72.22% and 27.79%, respectively and that in Group-2 was 75.56% and 24.44%, respectively, which was comparable, and statistically insignificant (p-value > 0.05).

Heart Rate

Table-4. Mean Heart Rate

Time intervals HR	Group1 (propofol -Ketamine)		Group2 (propofol -fentanyl)		p-value
	Mean	SD	Mean	SD	
Baseline	77.81	8.48	76.07	7.53	0.1463
Induction	85.17	8.83	69.47	6.59	0.0000
Intubation	87.28	8.57	74.24	6.72	0.0000
2 min after intubation	85.90	8.72	74.28	6.56	0.0000
5 min after intubation	84.10	9.40	75.27	6.81	0.0000
Incision	83.80	9.25	74.02	7.27	0.0000
2 min after incision	79.30	9.22	75.74	7.39	0.0048
5 min after incision	80.00	8.41	74.78	7.20	0.0000
15 min after incision	78.10	8.53	73.71	6.84	0.0002
30 min after incision	78.28	7.94	77.17	6.93	0.3187
45 min after incision	77.68	8.03	76.43	6.80	0.2625
60 min after incision	77.60	7.81	76.37	6.69	0.2884
Extubation	85.17	8.62	83.02	7.90	0.0836
10 min after extubation	87.92	9.93	83.68	11.20	0.0078
20 min after extubation	86.66	8.26	82.83	8.10	0.0020
30 min after extubation	84.50	7.88	82.08	6.71	0.0276
40 min after extubation	81.73	8.07	81.94	7.00	0.8515
50 min after extubation	81.06	7.24	80.37	7.44	0.5298
60 min after extubation	82.80	7.53	82.57	7.83	0.8387
Student's t-Test					

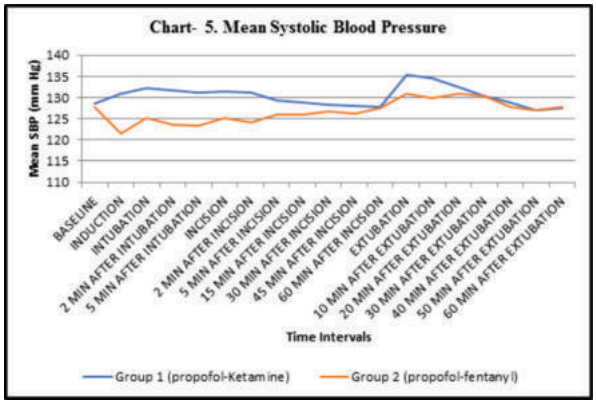


Mean baseline heart rate, in Group-1 was 77.81 bpm (beats per minute), where as in Group-2, it was 76.07 bpm, which was comparable and statistically insignificant (p value >0.05). Mean heart rate increased from baseline in Group-1, and decreased slightly in Group-2 following induction of anaesthesia. There was a return of heart rate towards baseline during maintenance period. In the initial phase of maintenance period the difference in heart rate was statistically significant. There was an in increase in heart rate after extubation which gradually returned back towards the baseline.

Systolic Blood Pressure

Table-5. Mean Systolic Blood Pressure

Time intervals SBP	Group1 (propofol -Ketamine)		Group2 (propofol -fentanyl)		p-value
	Mean	SD	Mean	SD	
Baseline	128.52	7.38	127.89	6.71	0.5477
Induction	130.93	7.19	121.51	7.28	0.0000
Intubation	132.34	7.33	125.14	7.50	0.0000
2 min after intubation	131.76	8.34	123.64	7.95	0.0000
5 min after intubation	131.21	8.33	123.26	6.67	0.0000
Incision	131.36	7.34	125.26	6.65	0.0000
2 min after incision	131.21	8.31	124.20	6.58	0.0000
5 min after incision	129.27	7.44	125.86	6.58	0.0013
15 min after incision	128.89	7.16	125.88	6.30	0.0031
30 min after incision	128.4	7.07	126.72	6.57	0.1009
45 min after incision	128.13	7.05	126.17	6.21	0.0496
60 min after incision	127.76	7.20	127.57	6.03	0.8603
Extubation	135.3	7.44	130.84	6.71	0.0000
10 min after extubation	134.46	8.61	129.96	7.55	0.0003
20 min after extubation	132.37	8.11	131.02	6.38	0.2181
30 min after extubation	130.4	8.11	130.47	6.24	0.9508
40 min after extubation	128.84	8.39	127.67	7.24	0.3147
50 min after extubation	126.88	8.27	127.00	7.29	0.9164
60 min after extubation	127.62	9.46	127.70	7.99	0.9525
Student's t-Test					



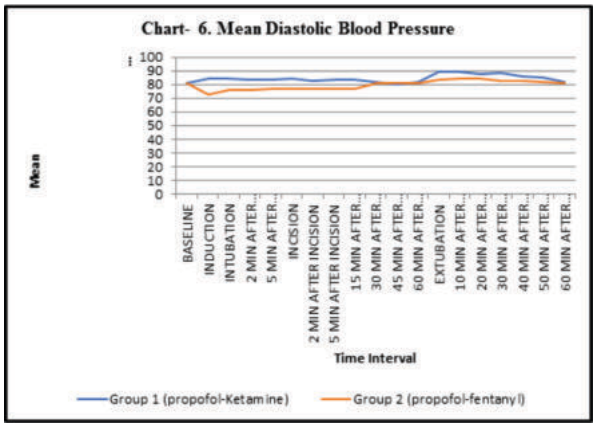
Baseline mean systolic blood pressures were comparable between the two groups. Mean systolic blood pressure increased in Group-1 after induction and intubation whereas it decreased in Group-2. The difference was statistically significant (p-value < 0.05). There was a gradual recovery towards baseline during maintenance period in both the groups. In the recovery period, the mean systolic blood pressure increased post-extubation in both the groups, returning towards baseline, gradually, over 60 minutes. The raise in blood pressure was more in Group-1 which was statistically significant (p value <0.05)

Diastolic Blood Pressure

Table-6. Mean Diastolic Blood Pressure

Time intervals DBP	Group1 (propofol -Ketamine)		Group2 (propofol -fentanyl)		p-value
	Mean	SD	Mean	SD	
Baseline	81.23	8.78	81.08	6.51	0.8928
Induction	84.70	9.10	72.36	6.03	0.0000
Intubation	84.93	8.72	75.96	6.17	0.0000
2 min after intubation	83.57	9.07	76.17	5.79	0.0000
5 min after intubation	83.14	8.88	76.64	6.12	0.0000
Incision	84.27	9.67	76.87	5.95	0.0000
2 min after incision	83.08	10.81	77.30	6.28	0.0000
5 min after incision	83.42	10.04	76.59	6.18	0.0000
15 min after incision	83.71	10.99	77.12	6.11	0.0000
30 min after incision	81.9	7.17	80.69	6.82	0.2471
45 min after incision	80.52	7.79	80.85	6.26	0.7539
60 min after incision	82.27	9.41	81.14	7.04	0.3952
Extubation	89.28	8.18	83.22	6.77	0.0000
10 min after extubation	89.43	9.25	84.68	7.06	0.0001
20 min after extubation	87.57	9.32	84.49	6.61	0.0114
30 min after extubation	88.14	8.96	83.12	7.79	0.0001

40 min after extubation	85.83	10.04	83.00	7.18	0.0308
50 min after extubation	85.39	9.15	82.03	7.11	0.0066
60 min after extubation	82.14	9.20	81.34	7.44	0.5221
Student's t-Test					

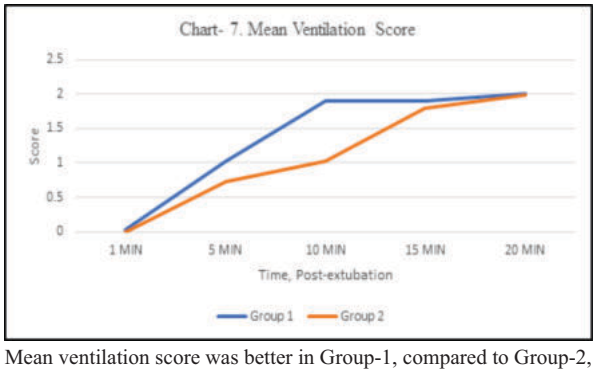


Baseline mean diastolic blood pressure between the two groups were comparable. After induction and intubation, mean diastolic blood pressure increased in Group-1 and decreased in Group-2 and the difference was statistically significant in the initial phase of maintenance period, with gradual fall towards baseline pressure in both the groups. In the recovery period, the mean diastolic blood pressure increased post-extubation in both the groups, returning towards baseline, gradually, over 60 minutes. The raise in blood pressure was more in Group-1 which was statistically significant (p value <0.05)

Ventilation Score.

Table-7. Mean Ventilation Score.

VENTILATION SCORE					
Time intervals	Group 1 (propofol-Ketamine)		Group 2 (propofol-fentanyl)		p-value
	Mean	SD	Mean	SD	
1 min	0.03	0.18	0.00	0.00	0.08
5 min	1.03	0.18	0.73	0.44	<0.05
10 min	1.90	0.30	1.03	0.18	<0.05
15 min	1.90	0.30	1.80	0.40	0.06
20 min	2.00	0.00	1.99	0.11	0.31
Student's t-Test					

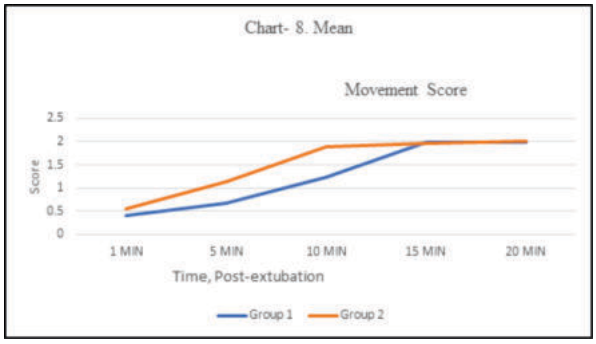


Mean ventilation score was better in Group-1, compared to Group-2, statistically significant till 10 minutes.

Movement Score.

Table-8. Mean Movement Score

MOVEMENT SCORE					
Time intervals	Group 1 (propofol-Ketamine)		Group 2 (propofol-fentanyl)		p-value
	Mean	SD	Mean	SD	
1 MIN	0.42	0.50	0.56	0.50	0.07
5 MIN	0.67	0.47	1.13	0.66	<0.05
10 MIN	1.23	0.43	1.90	0.30	<0.05
15 MIN	1.99	0.11	1.96	0.21	0.17
20 MIN	1.99	0.11	2.00	0.00	0.31
Student's t-Test					



Mean movement score was better in Group-2, compared to Group-1, statistically significant till 10 minutes.

Wakefulness Score.

Table-9. Mean Wakefulness Score

WAKEFULNESS SCORE					
Time intervals	Group 1 (propofol-ketamine)		Group 2 (propofol-fentanyl)		p-value
	Mean	SD	Mean	SD	
1 min	0.64	0.48	0.71	0.46	0.34
5 min	1.36	0.48	1.56	0.50	<0.05
10 min	1.69	0.47	1.91	0.29	<0.05
15 min	1.97	0.18	2.00	0.00	0.65
20 min	1.98	0.15	2.00	0.00	0.56
Student's t-Test					

Mean wakefulness score was better in Group-2, statistically significant till 10 minutes.

DISCUSSION

Effect On Heart Rate

Following induction with propofol and ketamine, an increase in heart rate from the baseline can be attributed to ketamine's sympathetic stimulation of the CNS. The increase in heart rate in both groups after extubation may have been brought on by the regaining of consciousness after the anaesthetic was stopped.

In a 1990 study by Mayer et al., who compared the hemodynamic and analgesic effects of propofol and fentanyl with those of propofol and ketamine, they discovered that the heart rate decreased more in the group to which propofol and fentanyl was administered than in the group treated with propofol and ketamine (Mayer et al., 1990). This is consistent with our research.

In a similar study conducted by Bajwa et al. 2010, heart rate increased during induction in the group in which propofol and ketamine combination was used whereas heart rate reduced in the group in which propofol and fentanyl was used. Also, heart rate increased in both the groups following extubation. These findings are in accordance with our study (Bajwa et al., 2010).

In the study comparing ketamine-propofol with fentanyl-propofol for short surgical procedures in pediatric patients conducted by Mahendra Kuttarmare et al., 2020, it was found that heart rate increased in the group receiving ketamine-propofol and decreased in the group receiving fentanyl-propofol (Mahendra Kuttarmare & Pande, 2020). A similar finding was observed by us in our study.

Effect On Systolic And Diastolic Blood Pressure

Though there was an increase in blood pressure in Group-1 following induction and intubation, the increase in blood pressure was small, indicating opposing action of propofol and ketamine on blood pressure. Due to the combined cardiodepressant action of both propofol and fentanyl the fall in blood pressure was steeper in Group-2 (Miller, 2020a, 2020b). As a result of the awakening response to intubation blood pressure was raised following extubation, which later returned to preoperative values (Bajwa et al., 2010).

Billard et al., 1994, found that propofol and fentanyl when used together causes more hypotension than propofol when used alone. They conducted a study on the hemodynamic response to induction and intubation with different doses propofol and fentanyl to determine their relationship. This is in accordance with the findings of our study (Billard et al., 1994).

Nalini et al., 2014, in their study comparing propofol and ketamine with propofol and fentanyl for puerperial sterilization under sedation with TIVA, recorded a drop in blood pressure with propofol and fentanyl infusion. We had noted a similar finding in our study (KB, 2014).

Akihiko Inoue et al., 2019, found an association between post-intubation hypertension with the use of ketamine compared to the use of propofol (Inoue et al., 2019).

In the study Tusharbhai et al., 2022, on comparison of propofol and ketamine with propofol and fentanyl as TIVA in maxillofacial surgeries recorded a drop in blood pressure in the propofol-fentanyl group. We also recorded a similar finding (Tusharbhai et al., 2022).

Recovery from anaesthesia (ventilation, movement and wakefulness)- Because ketamine, which also has a sympathomimetic action and inhibits bronchospasm, has a minor impact on breathing, Group 1 had better ventilation scores till 10 minutes (Rosenbaum et al., 2022). While both fentanyl and propofol are respiratory depressants (Sahinovic et al., 2018). We found that movement score was better in Group-2, compared to Group-1 till 10 minutes and wakefullness score was also better in Group-2 compared to Group-1, calculated by the Stewards post-anaesthetic recovery scoring system.[7] These findings were supported by similar results seen the study conducted by Bajwa et al (2010).

CONCLUSION

The results of this study allow us to draw the conclusion that the combinations of propofol plus ketamine or fentanyl produce rapid, comfortable, and safe anaesthesia with very minor hemodynamic alterations. The combination of propofol and fentanyl decreased stress reactions during laryngoscopy and intubation. During the maintenance phase, the propofol-ketamine and propofol-fentanyl combinations both displayed stable hemodynamics. Patients receiving propofol-fentanyl experienced a little decline in ventilation score during their recovery. In terms of wakefullness and movement, the propofol-fentanyl group fared better in terms of recovery. Due to their considerable metabolism, rapid elimination, and high total body clearance, both propofol-ketamine and propofol-fentanyl were found to be associated with a smooth and swift recovery in our study. Consequently, we can draw the conclusion that both of the drug combinations, propofol-ketamine and propofol-fentanyl, can be used in total intravenous anaesthesia for short elective surgeries because they provide effective surgical anaesthesia while putting little strain on hemodynamic parameters, maintaining stability and promoting quick and easy recovery.

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