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Original Research Article

Comparison of Three Different Doses of Ketamine-Propofol Combination in Short Surgical Procedures as Sedative and Analgesic

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ABSTRACT

Objectives: A comparison between three different doses of intravenous ketamine-propofol combination (equal strength) in short surgical cases with respect to adequate analgesia, sedation, Hemodynamic stability, Need for supplementation and Airway intervention.
Study design: Prospective Randomised study.
Materials and Methods: Ninety patients more than 18 years of age, fulfilling the inclusion criteria were included for the study after obtaining informed consent from them. Heart rate, blood pressure (systolic, diastolic and Mean Arterial Pressure), peripheral oxygen saturation and respiratory rate were recorded.
Results: The duration varied from 2 minutes to 27 minutes according to the procedure performed. Recovery period varied from 9 minutes to 33 minutes according to the total dosage used. We were able to maintain the adequate sedation and analgesia and surgeons continued the procedure without difficulty. There was minimal change in Mean Arterial Pressure and Heart Rate after giving the loading dose. Incremental doses did not result in additional airway intervention. Patients did not need airway assistance for more than 1 minute.
Conclusion: Ketamine propofol combination had provided a satisfactory anaesthesia for the patients who were posted for short surgical procedures like Incision and drainage, wound debridement and foreign body removal. Haemodynamics were stable throughout the procedure with this combination.

Key words: randomised, propofol, ketamine, haemodynamics.

INTRODUCTION

Short surgical procedures (duration of less than 30 minutes) done under local anaesthesia are very difficult and need patients co-operation to complete it. So surgeons prefer to do these procedures under sedation and analgesia. There are different combinations of anaesthetic drugs used for this purpose. Commonly used drugs are ketamine or propofol with midazolam or fentanyl in different combinations. The drawbacks are prolonged sedation, need for bag mask ventilation and emergence phenomenon (ketamine delirium) which commonly occurs with the routine dose.

Ketamine and propofol administered in various combinations have offered effective sedation for gynaecologic, ophthalmologic, and cardiovascular procedures in all age groups. The opposing hemodynamic and respiratory effects of each drug may enhance the utility of this drug combination, increasing both safety and efficacy and allowing reduction in the dose of propofol required to achieve

sedation. The addition of ketamine to propofol may counteract the cardio-respiratory depression seen when propofol is used alone, whereas propofol blunts the psychotomimetic and nauseant effects of ketamine. Further, the addition of ketamine to propofol provides an analgesic effect that is absent when propofol is used alone.

Recent study by Willman and Andolfatto [1] indicated that, a combination of ketamine and propofol in lower doses than routine provided an acceptable form of analgesia and sedation in short surgical procedures especially in emergency departments. It required less interruption with minimal side effects and gave high success rates.

A comparison between three different doses of intravenous ketamine-propofol combination (equal strength) in short surgical cases with respect to adequate analgesia, sedation, Hemodynamic stability, Need for supplementation and Airway intervention.

MATERIALS AND METHODS

This is a randomized, prospective study of 90 patients who underwent short surgical procedures in our emergency minor operation theatre after obtaining approval from hospital ethical committee. Informed written consent was obtained from all patients. They were divided into three groups, each consisted of thirty patients.

- Group KPL - Ketamine -Propofol - Low dose

(0.50 mg/kg of ketamine and 0.50 mg/kg of propofol)

- Group KPR - Ketamine -Propofol - Recommended dose

(0.75 mg/kg of ketamine and 0.75 mg/kg of propofol)

- Group KPH - Ketamine -Propofol - High dose

(1.0 mg/kg of ketamine and 1.0 mg/kg of propofol)

Inclusion criteria

- ASA I & II patients
- Either sex posted for short surgical procedures
- Approximate duration of 30 minutes and less
- Age group: 18 years and above

Exclusion criteria

- Age< 18 years
- Patients with full stomach
- History of allergy to ketamine or propofol
- Patients receiving narcotics or other analgesics preoperatively
- Patients with cardiovascular, renal or nervous systems disorders
- Patients with psychiatry problems.
- Pregnancy

Parameters Studied

- Heart rate
- Blood pressure (systolic, diastolic and mean arterial Pressure)
- Respiratory rate
- Oxygen saturation (SPO_2)
- Effective duration and Duration for recovery
- Airway management
- Emergence phenomena
- Vomiting

Ninety patients more than 18 years of age, fulfilling the inclusion criteria were included for the study after obtaining informed consent from them. Patients were allotted randomly into three groups (KPL, KPR and KPH), before entering the operation theatre.2ml of ketamine (100mg) with 1% propofol 10 ml was added and made up to 20ml in a syringe with distilled water. This had provided strength of 5mg/ml of ketamine and 5mg/ml of propofol in a same syringe (1:1 ratio).

The patients were thoroughly evaluated and examined. Pulse rate, blood pressure, heart rate were recorded before the procedure. An intravenous line was secured with venous cannula. 2 minutes prior to ketamine-propofol drug administration all patients were given a premedication of 0.2mg Glycopyrrolate intravenously.

According to the patient's group label, they were given the dose of ketamine-propofol for 1 minute. Heart rate, blood pressure (systolic, diastolic and Mean

Arterial Pressure), peripheral oxygen saturation and respiratory rate were recorded one minute prior and one minute after the ketamine-propofol administration. Then after every 5 minutes, parameters were recorded again up to 30 minutes.

Adequacy of sedation was analyzed using Ramsay sedation Scale. [2] Score of 5 and above was considered satisfactory and surgeon was allowed to do the procedure. Score of 4 and below was treated inadequate and given a supplemental dose of ketamine 0.25m/.kg plus propofol 0.25mg/kg as an increment (same prepared drug combination). Supplementation of ketamine - propofol was given till the patient achieves adequate depth of anaesthesia. If needed, more than one dose was also administered.

The effective duration was calculated from the time of administration of loading dose till the patient recovers from adequate sedation with Ramsay sedation scale of 4 and below. Need and number of supplementations were recorded. The recovery time was calculated from the time of loading dose till the patient to score more than 9 out of 10 in Aldrete Modified Recovery Score.

Requirement of airway intervention by means of oxygen supplementation by mask or assisted ventilation by bag mask was recorded. The duration of intervention required was also noted. Untoward events like vomiting or emergence phenomena during recovery was carefully watched and recorded.

Statistical analysis was done using Open Epic Version 2.2.1(Updated Jan 2010); Open Source Epidemiologic Statistics for Public Health of Emory University, USA. As for the qualitative variables, the significance of their occurrence was compared in terms of chi square test and for quantitative variables, t test was used. In all comparisons, a p value of < 0.05 was considered to be statistically significant.

RESULTS

Age

Minimum age was 18 yrs, Maximum age was 67 yrs. In KPL group, Mean age was 38±9.56 yrs; (Range=23-56), while mean age was 37.3±11.4 yrs; (Range=19-67) in KPR, and in KPH group, it was 37±12 (Range=18-61).There was no statistical difference between the groups (table-1).

Table 1: Age (in years)

	Min	Max	AVG	SD	P Value
KPL	23	56	38	9.56	0.956
KPR	19	67	37.3	11.4	
KPH	18	61	37	12	

Weight

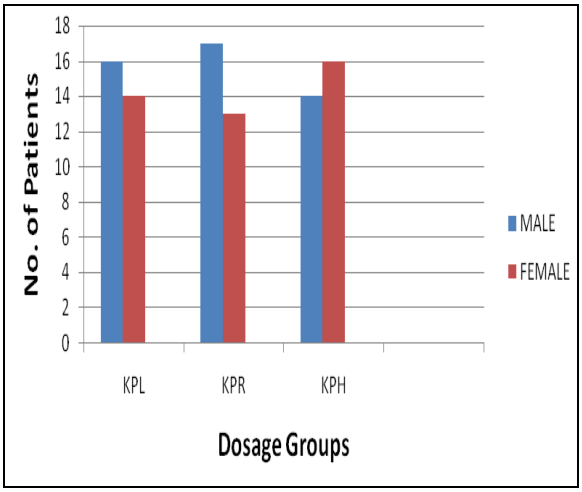
The weights of the patients of the three groups were comparable (table-2).The minimum weight (in kg) was 35 and maximum weight was 80 kg. The Mean±SD weights (in kg) of the groups were 51.07±10.68; 51.73±9.84; 51.30±8.79 in KPL, KPR and KPH respectively.

Table2: Weight (in kg)

	Min	Max	AVG	SD	P Value
KPL	35	80	51.07	10.68	0.956
KPR	39	69	51.73	9.84	
KPH	39	70	51.30	8.79	

Sex

Sex Distribution of each group is depicted in Graph-1, which indicates no difference among groups.



Graph 1: Sex

Loading Dose

The loading dose required was given as per the weight of the patient. It was 0.5mg/Kg in KPL, 0.75mg/Kg in KPR and 1.0mg/Kg in KPH. So accordingly the loading dose was 25.92±5.35mg in KPL,

39.83±7.57 mg in KPR (p<0.05) and 51.92±8.75 mg in KPH (p<0.05).

Effective Duration

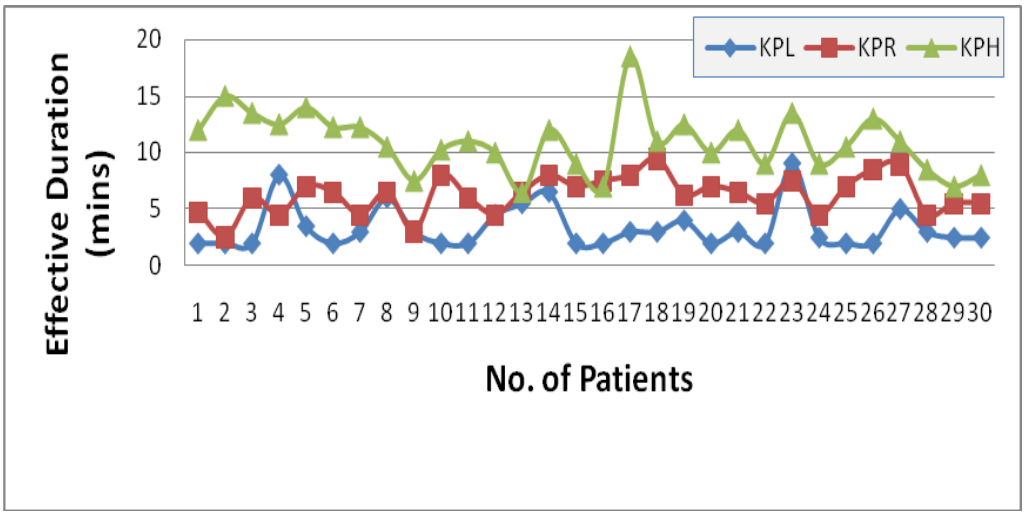
It was observed from table 3 and 4 that the effective duration of loading dose was 3.38±1.90 mins in KPL, 6.25±1.68 mins in KPR (p<0.05) and it significantly increased to 10.96±2.65 mins in KPH (p<0.05).

Table 3: KPL Vs KPR (Loading Dose)

Variables	Groups	No of individuals	MEAN & SD	P
Loading Dose(mg)	KPL	30	25.92±5.35	<0.05
	KPR	30	39.83±7.57	
Effective Duration(min)	KPL	30	3.38±1.90	<0.05
	KPR	30	6.25±1.68	
Incremental Dose(mg)	KPL	30	13.1±2.44	<0.05
	KPR	30	15.45±2.70	

Table 4: KPR Vs KPH (Loading Dose)

Variables	Groups	No of individuals	MEAN & SD	P
Loading dose(mg)	KPR	30	39.83±7.57	<0.05
	KPH	30	51.92±8.75	
Effective duration(min)	KPR	30	6.25±1.68	<0.05
	KPH	30	10.96±2.65	
Incremental dose(mg)	KPR	30	15.45±2.70	<0.05
	KPH	30	13.2±2.38	



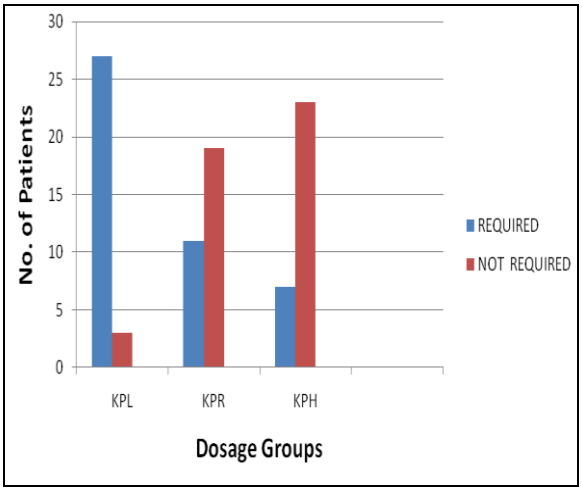
Graph 2: Effective Duration of Three Groups

Incremental Dose

It was noticed that the incremental dose required in 27 patients in KPL group, 11 patients in KPR group and only 7 patients in KPH group.

Significantly more number of patients in KPL group required incremental doses in comparison to KPR group (90% vs 36.66%, p<0.05). But there was not much difference between KPR and KPH group (36.66% vs 23.33%, p=0.26).

The amount of Ketamine and Propofol required in KPL was 13.1±2.44 mg, KPR was 15.45±2.7 mg in comparison to 13.2±2.38 mg (p<0.05) in KPH.

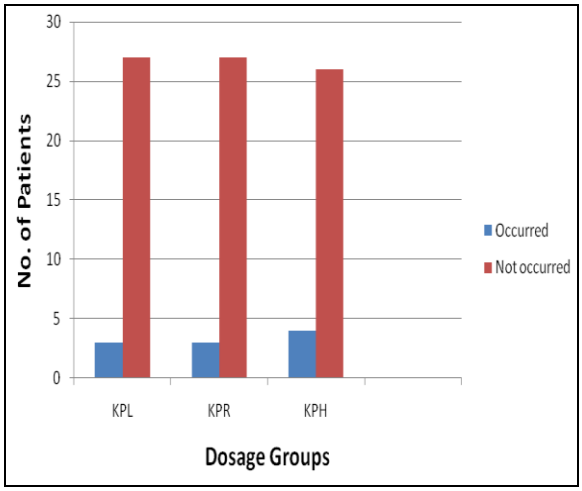


Graph 3: Comparison between three groups for incremental dose

Airway Intervention

Airway intervention was needed in some patients due to fall in oxygen saturation below 92%. None of the patients required airway intervention in KPL group, while 26.7% and 40% needed it in KPR and KPH group respectively.

Emergence



Graph 4: Comparison of emergence reaction in different groups

Repetition of words and hand movements were noticed in 3 patients each in KPL and KPR group, and 4 patients in KPH group suggesting no association between occurrence of emergence and dosage of the drug.

Vomiting

There was no incidence of post operative vomiting in any of the patients in any group.

Recovery Time

There was no difference in Recovery time between KPL and KPR groups; whereas it was significantly higher in KPH group ($p<0.05$), (range=25.5-14).

Table 5: KPL Vs KPR (Recovery Time)

Variables	Groups	No of individuals	Mean & SD	P
Recovery Time(min)	KPL	30	14.27±5.86	0.537
	KPR	30	13.48±3.77	

Table 6: KPR Vs KPH (recovery time)

Variables	Group	No of individuals	Mean & SD	P
Recovery Time(min)	KPR	30	13.48±3.77	<0.05
	KPH	30	19.46±2.99	

Effect on HR, MAP, RR, SPO_2

The mean and standard deviation of HR, MAP, RR and O_2 saturation of the three groups are tabulated in table 7, 8, 9 and 10.

Table 7: Comparison of HR, MAP, RR, SPO2 KPL Vs KPR

Variables	Groups	0 Min		1 Min		6 Min	
		MEAN±SD	P	MEAN±SD	P	MEAN±SD	P
HR(min^{-1})	KPL	93.1±9.11	0.572	94.53±8.29	0.797	95.13±8.78	0.788
	KPR	91.77±9.02		93.93±9.70		94.47±10.12	
MAP(mm of Hg)	KPL	86.77±9.80	0.986	85.40±49	<0.05	86.80±10.11	0.156
	KPR	86.73±9.04		57.63±9.74		90.11±7.93	
RR(min^{-1})	KPL	16.77±2.30	0.913	14.90±2.64	0.760	15.73±2.49	0.621
	KPR	16.83±1.93		14.70±2.42		15.47±1.43	
O_2 (%)	KPL	98.87±1.22	0.420	96.97±2.11	0.187	98.03±1.75	0.926
	KPR	99.10±0.96		95.967±3.54		98.00±1.68	

Table 8: Comparison of HR, MAP, RR, SPO2 KPR Vs KPH

Variables	Groups	0 min		1 min		6 min	
		MEAN±SD	P	MEAN±SD	P	MEAN±SD	P
HR(min^{-1})	KPR	91.77±9.02	0.832	93.93±9.70	0.985	94.47±10.12	0.546
	KPH	91.30±8.12		93.97±7.51		95.83±6.93	
MAP(mm Hg)	KPR	86.73±9.04	0.527	57.63±9.74	<0.05	90.11±7.93	<0.05
	KPH	88.07±7.19		92.87±8.76		95.20±8.75	
RR(min^{-1})	KPR	16.83±1.93	0.411	14.70±2.42	0.097	15.47±1.43	0.724
	KPH	17.27±2.18		13.43±3.35		15.33±1.63	
SO_2 (%)	KPR	99.10±0.96	0.144	95.967±3.54	<0.05	98.00±1.68	<0.05
	KPH	98.63±1.45		94.167±3.14		96.80±1.45	

Heart Rate

There was not much difference in the baseline heart rate of the three groups. However there was a fall in the heart rate when the dose was increased from KPL to KPR; but the heart rate did not change significantly at 0, 1, 6 minutes in the three groups.

Mean Arterial Pressure

There was not much change in mean arterial pressure at 0, 1, 6 minutes in KPL and KPR groups. This was in contrast to the KPH group where the mean arterial pressure increased from 88.07 to 92.87 from KPL to KPR and then from 92.87 to 95.20 from KPR to KPH.

Table 9: Comparison of HR, MAP, RR, and SPO2 in different groups at 0 and i minute

Variables		KPL		KPR		KPH	
		MEAN±SD	P	MEAN±SD	P	MEAN±SD	P
HR	0 MIN	93.1±9.11	0.527	91.77±9.02	0.375	91.30±8.12	0.191
	1 MIN	94.53±8.29		93.93±9.70		93.97±7.51	
MAP	0 MIN	86.77±9.80	0.603	86.73±9.04	<0.05	88.07±7.19	<0.05
	1 MIN	85.40±10.49		57.63±9.74		92.87±8.76	
RR	0 MIN	16.77±2.30	<0.05	16.83±1.93	<0.05	17.27±2.18	<0.05
	1 MIN	14.90±2.64		14.70±2.42		15.47±1.43	
O_2	0 MIN	98.87±1.22	<0.05	99.10±0.96	<0.05	98.63±1.45	<0.05
	1 MIN	96.97±2.11		95.967±3.54		94.167±3.14	

Table 10: Comparisons of HR, MAP, RR, and SPO2 in different groups at 1 and 6 minute

Variables		KPL		KPR		KPH	
		MEAN±SD	P	MEAN±SD	P	MEAN±SD	P
HR	1 MIN	94.53±8.29	0.786	93.93±9.70	0.83	93.97±7.51	0.322
	6 MIN	95.13±8.78		94.47±10.12	3	95.83±6.93	
MAP	1 MIN	85.40±10.49	0.600	87.63±9.74	0.28	92.87±8.76	0.306
	6 MIN	86.80±10.11		90.11±7.93	3	95.20±8.75	
RR	1 MIN	14.90±2.64	0.215	14.70±2.42	0.13	15.47±1.43	0.724
	6 MIN	15.73±2.49		15.47±1.43	8	15.33±1.63	
O_2	1 MIN	96.97±2.11	<0.05	95.967±3.38	<0.	94.167±3.14	<0.05
	6 MIN	98.03±1.05		98.00±1.68	05	96.80±1.45	

Respiration rate

The respiration rate decreased in all the three groups after giving the loading dose which normalized within 6 minutes. There was no significant difference in respiration rate among the groups.

Oxygen saturation

Significant difference was observed in oxygen saturation which decreased after giving the loading dose but again normalized at 6 minutes. In KPH, oxygen saturation has decreased to less than 92% in 12 patients, out of which 3 required assisted ventilation. However no patient required assisted ventilation in KPR and KPL.

DISCUSSION

General Anaesthesia for short surgical procedures is most commonly carried out with ketamine or propofol in addition with opioids and benzodiazepines. Ketamine commonly produces emergence delirium and vomiting along with increase in heart rate and blood pressure in the routine induction dose. Propofol at induction dose can result in severe fall in blood pressure and does not have any analgesic property. It is deleterious to a patient posted for emergency without much stabilization with the above drugs in regular doses when used separately. In the present study, ketamine and propofol were combined to get the additive effect and minimize the side effects of both.

The study was performed on the patients who underwent short surgical procedures in emergency operation theatre. A low dose and a high dose of ketamine-propofol combination were compared with recommended dose, based on the study done by Willman and Andolfatto. [1]

Effective Duration

After 0.2mg of glycopyrrolate as a premedication, the patients were given the calculated loading dose of drug combination for 1 minute. The effective duration was calculated till the patient maintained Ramsay Sedation Scale of 5 and more. In KPL group the duration varied from 2 to 9 minutes with a mean of 3.38±1.90 minutes. It was 2.5 to 9.5 minutes with a mean of 6.25±1.68 minutes in group KPR and 6.5 to 18.5 minutes w it a mean of 10.96±2.65 minutes in KPH group. The above values showed uniform increase in effective duration with increased bolus dosage.

Procedure duration

The mean duration of procedures was 8.41±5.99 min (KPL), 6.75±3.52 min (KPR) and 9.46±3.28 min (KPH). It does not show any significant difference and comparable within three groups. The duration varied from 2 minutes to 27 minutes according to the procedure performed. Group KPL needed more number of additional doses of drug to complete the procedure. Many patients reacted to pain within 2 to 3 minutes and it was difficult to maintain with 0.5 mg/kg (KPL) dose alone.

Incision and drainage procedure had taken minimal duration and procedures like slough excision and foreign body removal took longer time. The other procedures done were wound debridement, decompression of compartment syndrome and abscess drainage

Recovery duration

Recovery time was calculated from the time of loading dose till the patient achieved a score of more than 9 in Andretti modified recovery Score. The mean duration was 14.27±5.86minutes in KPL group, 13.48±3.77minutes in KPR group and 19.46±2.99 minutes in KPH group. This duration was low in KPR group than other two groups. But it is not considered as a significant one, as patients were given supplementation of ketamine-propofol whenever it was required. Once the effective duration was over, the groups behave differently as the total dose differs to each patient. Recovery period varied from 9 minutes to 33 minutes according to the total dosage used. The maximum dose required for procedures less than 30 minutes was not more than 1.25mg/kg of ketamine-propofol each. This was comparable to study by Kalpana Vora and co-workers, [3] Erkan Tomatir and co workers, [4] Schuttler and co workers. [5]

Supplementation

An incremental dose of 0.25mg/kg of ketamine propofol combination was given when the patient was not able to maintain Ramsay sedation scale of 5 and more. We were able to maintain the adequate sedation and analgesia and surgeons continued the procedure without difficulty. No other drugs were needed. Twenty seven patients in group KPL required first increment (total dose of 0.75 mg/kg) and 4 patients required second increment (total dose of 1.0 mg/kg). 11 patients in group KPR required first increment. 7 patients in group KPH required first increment (total dose of 1.25 mg/kg).

Haemodynamics

There was minimal change in Mean Arterial Pressure and Heart Rate after giving the loading dose in the groups. There was a 1.5% decrease in Mean Arterial Pressure at one minute after loading dose in KPL group. There was a 2.3% increase in Heart Rate at one minute and 2.9% increase in heart rate at 6minute after the loading dose in KPR group, while the increase in heart rate was 2.9% and 4.9% at 1 and 6 min respectively in KPH group. These changes were very minimal and did not affect the patient's stability. It gives the inference that with the above combination of ketamine and propofol the Mean Arterial Pressure and Heart Rate did not vary much from baseline values. It gave good haemodynamic stability in all three groups. This was comparable to studies made by Morse and co-workers, [6] Nonaka and Suzuki, [7] Hernandez and Parramon, [8] Guit et al. [9]

Airway Intervention

Patient's respiration was observed carefully and peripheral oxygen saturation was monitored. Airway supplementation in the form of oxygen by mask was instituted only when saturation falls below 92%. Patients were ventilated with bag mask when required.

KPL group did not need any form of oxygen supplementation as the saturation was well maintained above 92% in all occasions. But all the patients in this group had a minimal fall in saturation of 2 to 5% after the loading dose of drug combination. It may be probably due to the action of propofol even with this small dose (0.5mg/kg). This dosage group did not need any airway intervention. At the same time it

did not provide adequate duration for the surgical procedure and required supplements.

Eight among the 30 patients in KPR group required supplementation of oxygen through mask as saturation decreased to less than 92% after giving the loading dose but none of them required assisted ventilation. 12 patients in KPH group needed oxygen supplementation by mask and 3 of them required bag and mask ventilation. Incremental doses did not result in additional airway intervention. Patients did not need airway assistance for more than 1 minute.

Increase in loading dose resulted in more airway intervention. But none of the patients required intubation for securing airway. All the patients in three groups invariably developed minimal airway depression. Ketamine has no influence on the incidence of apnea after propofol which is comparable with the study done by Hui and co workers. [10] But Mortero and co workers [11] had demonstrated that post operative PCO_2 level is more favorable with propofol ketamine combination rather than with propofol alone. Our study also showed that only minimal requirement for airway intervention is needed for a transient period. This was comparable to study made by Mortero and co workers. [11]

Other Side Effects

Emergence reaction (delirium) during recovery in the form of confusion, shouting, irrelevant talks and repeated hand movements were noted with 3(10%), 3(10%) and 4(13%) patients in KPL, KPR and KPH groups respectively. But all the above patients settled within one hour from the time of loading dose. They did not require any additional medications to overcome these phenomena. Combination with propofol has reduced the incidence and intensity of emergency delirium. Early return of cognitive function is comparable with the studies by Mortero and co workers [11] and Scigninano and co workers. [12]

Patients did not experience pain during injection. None of the patients developed nausea or vomiting in the post operative period.

In brief, Ketamine propofol combination had provided a satisfactory anaesthesia for the patients who were posted for short surgical procedures like Incision and drainage, wound debridement and foreign body removal. Haemodynamics were stable throughout the procedure with this combination. Among the three different doses, KPL did not provide adequate anaesthesia and other two groups, KPR and KPH provided a mean effective duration of 6 and 11 minutes respectively. All the procedures were done with minimal side effects. This was comparable to the study made by Hui and co workers, [10] Furuya and co workers, [13] Tosun and co workers [14] and Joho Tokumine et al, [15] Gray and co workers [16] and Friedberg, [17] Badrinath and co-workers, [18] Hamdani and Khan,[19] Tosun and co workers, [20] Gamal T. Yousef and Khalid M. Elsayed, [21] Ozgur Yagan et al, [22] Mohan C Mandal and co workers. [23]

CONCLUSION

The following are the conclusions of our study with Ketamine Propofol combination in same syringe in equal strength for three different doses.

1. KPR ($0.75mg.kg^{-1}$) and KPH ($1.0mg.kg^{-1}$) groups provided adequate analgesia and sedation with less need for supplementation. They can be used for the procedures of duration of less than 10 minutes.
2. Extension of procedure can be easily carried out with incremental doses ($0.25mg.kg^{-1}$) of same ketamine Propofol combination with respect to patient's reaction to stimulus.
3. The haemodynamics were stable in all dosage groups except oxygen saturation which decreased after the loading dose but again normalized within next 5 minutes.
4. None of the patients experienced pain during intravenous injection.

5. Recovery duration was increased with high total dosage.
6. Airway intervention was needed increasingly with high doses. None of the patients required intubation.
7. Emergence reaction had occurred with all three groups with very less degree of disturbance to patients. There is no correlation with total dosage.
8. Vomiting did not occur in any of the patients of any group.
9. Patients were devoid of awareness during the procedure.

The study concludes that a dose of 0.75 mg/kg to 1.0 mg/kg of ketamine propofol combination in same syringe can be used initially followed by fixed incremental doses of 0.25 mg/kg whenever needed. It was with minimal side effects and good haemodynamic stability for short surgical procedures like incision and drainage, decompression and wound debridement. But airway support should be kept in readiness.

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