Original Article

Procedural Sedation & Analgesia by Ketamine-Propofol (Ketofol) And Ketamine-Diazepam Combination In Day Case Surgery - A Comparative Study

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Abstract

Introduction: *Traditionally Procedural Sedation and Analgesia (PSA) is provided by various drugs and its combinations with mixed effect regarding safety and efficacy.*

Objective: *The aim of the study was to compare the combination of Ketamine & Propofol (Ketofol) and Ketamine-Diazepam for PSA in day case surgery.*

Materials & Methods: *This prospective study was carried out in CMH Dhaka on sixty patients equally divided in two groups between the period of May 2015 to September 2015. Group I patients received Injection Ketamine 1mg/kg & Injection Propofol 1mg/kg combination while group II patients received Injection Ketamine 2mg/kg & Injection Diazepam 0.2mg/kg combination. Clinical parameters like pulse rate, non invasive blood pressure (NIBP), percentage saturation of oxygen (SpO_2) were monitored, recorded and analyzed. Recovery was assessed by Aldred Recovery Score (ARS) and compared between groups.*

Results: *Rise of heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP) were statistically significant in group II patients when compared to group I both during the procedure & recovery but rise of mean arterial pressure (MAP) was significant only during procedure. The recovery time in group II patients (24.7 ± 3.6 min) was significantly higher (29.7 ± 4.1 min) than group I patients. Side effects like excessive bronchial secretion and postoperative agitation were also significantly lesser in Ketofol group.*

Conclusion: *Ketofol provides safer and more effective sedation and analgesia than Ketamine and Diazepam combination.*

Keywords: *Ketofol, Procedural sedation and analgesia, Day case surgery.*

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Introduction

Procedural sedation is a technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allows the patient to tolerate unpleasant procedures while maintaining cardiorespiratory function. Procedural Sedation and Analgesia (PSA) is intended to result in a depressed level of consciousness that allows the patient to maintain oxygenation and airway control independently[1,2]. Various drugs are available and used to provide procedural sedation like Benzodiazepines, Opioids, Ketamine, Propofol, Etomidate etc. either alone or in combinations. Minimal stress, maximum comfort, early recovery & early ambulation are the principle of selecting drugs for PSA or day case surgery. But every drug or combination of drugs has got its own merits and demerits. The objective of the study is to compare the effectiveness and safety of traditional combination of Ketamine and Propofol (Ketofol) for PSA in day case surgery.

Materials and Methods

It was a prospective, double blinded, comparative study carried in Combined Military Hospital (CMH) Dhaka, between the period of May 2015 to September 2015 after getting approval from hospital ethical committee.

Sixty patients scheduled for elective day case procedure were randomly selected for the study. Adult patients of age group 18-45 years from both

sexes of ASA status I & II, undergoing procedures of less than one hour duration were induced in the study. Patients with history of cerebrovascular disease (CVD), ischemic heart disease (IHD), raised intra cranial pressure (ICP), hypertension, seizure disorder, pregnancy or known hypersensitivity reaction to Ketamine, Propofol or Diazepam were excluded from the study. After taking informed written consent from all patients they were divided into two equal groups of thirty by lottery method. All patients were pre medicated with injection Ondansetron 8 mg IV. Group I patients received injection Ketamine 1 mg/k & injection Propofol 1mg/kg mixed in a single syringe and diluted with same amount with distilled water as a bolus whereas group II patients received injection Ketamine 2mg/kg & injection Diazepam 0.2 mg/kg combined as a bolus and diluted with distilled water and intra lipid (for double blinding) making 10 ml solution. All patients were oxygenated in requirement basis at a rate of 4 L/ minute by face mask. Heart rate, noninvasive blood pressure (NIBP), respiratory rate, Electrocardiogram (ECG), percentage saturation of oxygen (SpO_2) were monitored during procedure & during recovery at every 5 minutes interval. Ramsay Sedation Scale (RSS)[3] was monitored throughout the procedure by incremental doses of (25% of initial dose) as per requirement. Quality of analgesia was assessed by haemodynamics, sweating and respiratory rate. Aldrede recovery score[4] (>= 8) was used to ascertain recovery. Peroperative & postoperative (up to 6 hours) all complications were also recorded. All data were compiled in a preformed data sheet and analyzed by students't' test, two proportion test & chi square test. P value < 0.05 was considered significant.

Results

There was no significant difference regarding patient's characteristics like age, sex, weight and ASA grading (Table I).

There were predominance of orthopaedic and gynaecological procedures in both groups such as, close reduction of fractured bones or dislocated joints, dilatation & curettage, incision & drainage

Table I *Patients' characteristics*

Characteristics	Group I (n=30) Mean±SD	Group II (n=30) Mean±SD	p value	Result
Age (years)	34.73 ± 9.04	32 ± 7.1	0.2	NS (Student 'T' test, unpaired)
Weight (Kg)	60.8 ± 9.75	58.26 ± 7.82	0.4	NS (Student 'T' test, unpaired)
Sex- Male :Female	17:13	16:14	0.8	NS(Chi square test)
ASA Grading I/ II	20(66.66%)/	22(73.33%)	0.7	NS(Chi square test)
	10(33.33%)	/8(26.66%)	0.6	NS(Chi square test)

Table II *Type of procedure*

	Group I		Group II	
Surgical Procedure	Number	%	Number	%
Amputation of little finger	1	3.3%	1	3.3%
Cervical polypectomy	1	3.3%	1	3.3%
Close reduction of joints	7	23.3%	6	20.0%
Dilatation & Curettage (D&C)	6	20.0%	5	16.7%
Incision and Drainage of Abscess	7	23.3%	4	13.3%
Repair of tendon	2	6.7%	3	10.0%
Surgical toileting & repair	2	6.7%	2	6.7%
Wound debridement and dressing	2	6.7%	2	6.7%
Excision Biopsy	2	6.7%	6	20.0%
Total	30		30	

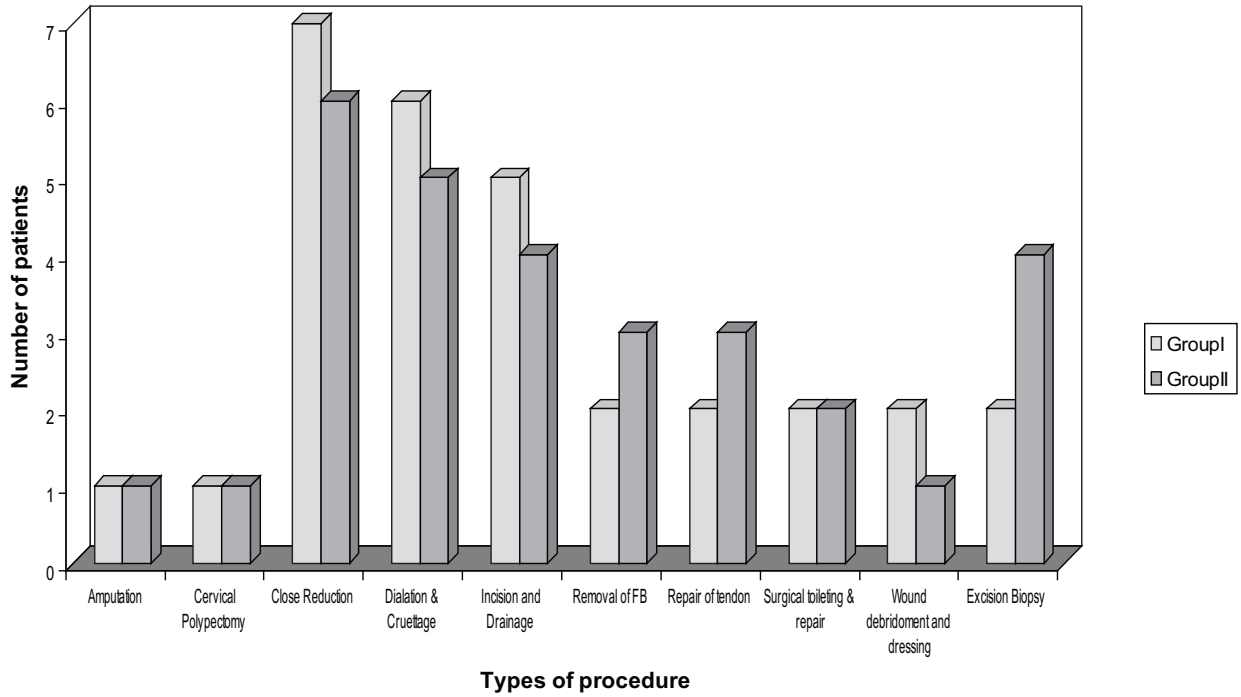

Figure I Types of procedure undertaken

Changes in heart rate are shown in table III. The mean of the value of during procedure and during recovery was first calculated and considered as mean ± SD of the values. As expected heart rate increased in patients of both groups during the procedure, during recovery but when compared between two groups it was significantly higher in group II patients as shown in table-III.

Table-III *Heart rate in two groups*

Time	Group I (n=30)	Group II (n=30)	p value	Result
Pre induction	77.9 ± 9.84	78.1± 11.43	0.86	NS (Student's 'T' test, unpaired)
After induction	82.35±3.65	88.45±4.84	0.90	NS (Student's 'T' test, unpaird)
5 minutes	84.2 ± 3.75	110 ± 10.4	0.04	S (Student's 'T' test, unpaired)
10 minutes	89.80±5.05	116.60±5.90	0.03	S (Student's 'T' test, unpaired)
15 minutes	89.9 ± 9.97	117.6 ± 7.05	0.03	S (Student's 'T' test, unpaired)
20 minutes	87.88±6.70	112.15±5.65	0.04	S (Student's 'T' test, unpaired)
25 minutes	84.44±64	100.94±6.55	0.05	S (Student's 'T' test, unpaired)
30 minutes	77.1±3.94	88.63±9.62	0.08	NS (Student's 'T' test, unpaired)

Values are presented as mean ± SD. Analysis was done by Student's 't' test. NS: Not significance p>0.05 (among two groups). Sig: Significant p<0.05 (among two groups).

Although the base line Blood Pressure (systolic, diastolic & mean) were quite similar in two groups but they were raised during the procedure and remained higher during recovery. In group II patients the rise of systolic & diastolic blood pressure were significantly higher during the procedure and during recovery (P<0.05), when compared to group I patients (Table IV, V).

Table IV *Systolic blood pressure in two groups*

Time	Group I (n=30)	Group II (n=30)	p value	Result
Pre induction	117.9 ± 9.84	118.1± 11.43	0.86	NS (Student's 'T' test, unpaired)
After induction	118.35±3.65	126.45±4.84	0.20	NS (Student's 'T' test, unpaired)
5 minutes	117.2 ± 3.75	138 ± 10.4	0.04	S (Student's 'T' test, unpaired)
10 minutes	119.80±5.05	146.60±5.90	0.03	S (Student's 'T' test, unpaired)
15 minutes	117.9 ± 9.97	137.6 ± 7.05	0.03	S (Student's 'T' test, unpaired)
20 minutes	115.88±6.70	132.15±5.65	0.04	S (Student's 'T' test, unpaired)
25 minutes	114.44±64	127.94±6.55	0.05	S (Student's 'T' test, unpaired)
30 minutes	117.1±3.94	121.63±9.62	0.08	NS (Student's 'T' test, unpaired)

Values are presented as mean ± SD. Analysis was done by Student's 't' test. NS: Not significance p>0.05 (among two groups). S : Significant p<0.05 (among two groups).

Table V *Diastolic blood pressure in two groups*

Time	Group I (n=30)	Group II (n=30)	p value	Result
Pre induction	77.9 ± 9.84	78.1± 11.43	0.86	NS (Student's 'T' test, unpaired)
After induction	78.35±3.65	79.45±4.84	0.90	NS (Student's 'T' test, unpaired)
5 minutes	77.2 ± 3.75	88 ± 10.4	0.04	S (Student's 'T' test, unpaired)
10 minutes	74.80±5.05	86.60±5.90	0.03	S (Student's 'T' test, unpaired)
15 minutes	77.9 ± 9.97	87.6 ± 7.05	0.03	S (Student's 'T' test, unpaired)
20 minutes	75.88±6.70	85.15±5.65	0.04	S (Student's 'T' test, unpaired)
25 minutes	74.44±64	83.94±6.55	0.05	S (Student's 'T' test, unpaired)
30 minutes	76.1±3.94	81.63±9.62	0.08	NS (Student's 'T' test, unpaired)

Values are presented as mean ± SD. Analysis was done by Student's 't' test. NS: Not significance p>0.05 (among two groups). S: Significant p<0.05 (among two groups).

But the mean blood pressure was significantly higher only during the procedure in group II patients (P<0.05) when compared to group I patients (Table: VI)).

Table VI *Mean blood pressure in two groups*

Time	Group I (n=30)	Group II (n=30)	p value	Result
Pre induction	87.9 ± 9.84	88.1± 11.43	0.86	NS (Student's 'T' test, unpaired)
After induction	88.35±3.65	89.45±4.84	0.90	NS (Student's 'T' test, unpaired)
5 minutes	87.2 ± 3.75	100 ± 10.4	0.04	S (Student's 'T' test, unpaired)
10 minutes	84.80±5.05	106.60±5.90	0.03	S (Student's 'T' test, unpaired)
15 minutes	87.9 ± 9.97	107.6 ± 7.05	0.03	S (Student's 'T' test, unpaired)
20 minutes	85.88±6.70	105.15±5.65	0.04	S (Student's 'T' test, unpaired)
25 minutes	84.44±64	103.94±6.55	0.05	S (Student's 'T' test, unpaired)
30 minutes	86.1±3.94	101.63±9.62	0.05	S (Student's 'T' test, unpaired)

Values are presented as mean ± SD. Analysis was done by Student's 't' test. NS: Not significance p>0.05 (among two groups). S: Significant p<0.05 (among two groups).

There was no significant difference in respiratory rate between two groups although increased respiration observed in both groups during induction which subsequently came down to baseline level during recovery (Table: VII).

Table VII *Respiratory rate in two groups*

Time	Group I (n=30)	Group II (n=30)	p value	Result
Pre induction	16.9 ± 9.84	15.1± 1.43	0.86	NS (Student's 'T' test, unpaired)
After induction	15±3.65	16.45±1.84	0.90	NS (Student's 'T' test, unpaired)
5 minutes	14.2 ± 3.75	14 ± 10.4	0.94	NS (Student's 'T' test, unpaired)
10 minutes	14.80±5.05	16.60±5.90	0.30	NS (Student's 'T' test, unpaired)
15 minutes	15.9 ± 9.97	17.6 ± 7.05	0.35	NS (Student's 'T' test, unpaired)
20 minutes	15.88±6.70	15.15±5.65	0.40	NS (Student's 'T' test, unpaired)
25 minutes	14.44±64	13.94±6.55	0.50	NS (Student's 'T' test, unpaired)
30 minutes	16.1±3.94	16.63±9.62	0.45	NS (Student's 'T' test, unpaired)

Values are presented as mean ± SD. Analysis was done by Student's 't' test. NS: Not significance p>0.05 (among two groups). S: Significant p<0.05 (among two groups).

The mean time required to complete the procedure was (20.2 ± 8.9) minute in group I and (24.7± 9.71) minute in group II & the difference was not statistically significant (Table: VIII).

Table VIII *Procedure time in two groups*

Time	Group I (n=30)	Group II (n=30)	p value	Result
Procedure time	20.2 ± 8.9	19.83 ± 9.71	0.75	NS (Student's 'T' test, unpaired)

Values are presented as mean ± SD. Analysis was done by Student's 't' test. NS: Not significant p>0.05 (among two groups). Sig: Significant p<0.05 (among two groups).

The recovery time in group I patients was (24.7 ± 3.6) min and (29.7 ± 4.1) min in group II patients and the difference was statistically significant (P<0.05) (Table: IX).

Table IX *Recovery time in two groups*

Time	Group I (n=30)	Group II (n=30)	p value	Result
Recovery time	24.7 ± 3.6	29.7 ± 4.1	0.02 S	(Student's 'T' test, unpaired)

Values are presented as mean ± SD. Analysis was done by Student's 't' test.NS: Not significance p>0.05 (among two groups). Sig: Significant p<0.05 (among two groups).

Immediately after recovery the differences of recovery score found statistically not significant between groups but was significant later (Table: X)

Table X *Average recovery score in two groups*

Time	Group I (n=30)	Group II (n=30)	p value	Result
After 10 minutes	6.93 ± 0.78	6.87 ± 0.73	1.00	NS (Student's 'T' test, unpaired)
After 20 minutes	8.93 ± 0.78	7.87 ± 0.73	0.01	S (Student's 'T' test, unpaired)
After 30 minutes	9.96 ± 0.21	8.28 ± 0.48	0.02	S (Student's 'T' test, unpaired)

Values are presented as mean ± SD. Analysis was done by Student's 't' test.
NS: Not significance p>0.05 (among two groups). Sig: Significant p<0.05 (among two groups).

There were few drug related complications in both groups during procedure and recovery. Twenty four patients (80%) had raised BP and twenty three of them also developed tachycardia in group II while these incidences were negligible in group I patients (Table: XI). Although none of them required any extra medication to combat these haemodynamic changes. Eight patients of group II had profuse bronchial secretion compared to three of group I who were treated with injection Atropine 0.02mg/kg body weight. Frequency of desaturation (Spo2< 90%) was more on group I. Difference between the groups regarding complication was statistically significant (Table: XI).

Table XI *Complications during procedure in two groups*

	Group I		Group II		P	Result
	Count	%	Count	%	value	
High blood pressure	7	23.3%	24	80.0	0.02	S(Chi square) test)
Tachycardia	6	20.0%		23	76.7	(Student's'T' test, unpaired)
Profuse secretion	3	10.0		8	26.7	
Desaturation	4	13.3%		2	6.7	

During recovery 11 patients (36%) developed recovery agitation in group II but 3 patients (10%) in group I. All of them were further sedated with Injection Midazolam. Mean BP remained higher than the baseline in 4 patients (3.3%) in group I. The differences of recovery agitation and raised mean blood pressure (MBP) between two groups were statistically significant (Table: XII). Few patients of both groups experienced post-operative nausea & vomiting but the incidences were not statistically significant.

Table XII *Complications during recovery in two groups*

	Group I		Group II		p	Result
	Count	%	Count	%	value	
Recovery agitation	3	10.0%	11	36.7%	0.042	S(Chi square)
Profuse secretion	1	3.3%	3	10.0%		
Vomiting	3	10.0%	2	6.7%		
High blood pressure	1	3.3%	4	13.3%		
Nausea	2	6.7%	2	6.7%		

Average cost required for Ketofol group (Taka 76.60 ± 17.50) was significantly higher than that of group II (Ketamine + Diazepam) patients (Taka 29.43 ± 6.23) (Table XIII).

Table XIII *Average cost of sedation in two groups*

Time	Group I (n=30)	Group II (n=30)	p value	Result
Cost of sedation	Tk 76.60 ± 17.52	TK29.43 ± 6.23	0.05	S(Chi square test)

Discussion

This study shows that ketofol is an effective and apparently safe drug for PSA in day case surgery. ketamine and propofol are physiologically compatible when administered together, the mixture of ketamine and propofol in a single syringe in 1:1 ratio offers a simple practical approach to medication in preparation and use[5]. Ketofol can be used in patients of all ages and with a broad range of acute and chronic co-morbid conditions with a wide safety limit and high level of patient satisfaction which highlights its versatility in the short minimally invasive procedure in emergency department or day case surgery[6]. In this study ketamine is mixed with propofol in sub anaesthetic dose which complements the effect of each drug. Mean dose of ketofol required to produce induction is 0.75 mg/kg of ketamine and propofol each, subsequent top up dose (0.25 mg/kg) given as and when required depending on length of the procedure. However, two patients of ketofol group (group 1) required larger than the mean dose of ketofol which may be due to the extent of tissue trauma, type of procedure or individual patient variation which simulates the other studies[6,7].

The sign of pain in group 1 patients as evaluated by tachycardia, tachypnoea, hypertension, sweating, movements were absent or insignificant unlike in group II patients as found in the study. The results are consistent with Furdya et al[8] & Hui et al[(9)] who suggested that minimal change observed in arterial pressure may be dose related and opposite action of ketamine and propofol on hemodynamic system.

Aboeldahab H et al[10] studied on sixty patients and compared the hemodynamic status between propofol ketamine and their combination as induction agent and found that MAP decreased in propofol group, increased in ketamine group and remains comparable to baseline in ketofol group and the differences were statistically significant. Akon A et al[11] published a trail of sixty patients between one month and thirteen years of age undergoing cardiac catheterization received sedation with propofol and or ketofol (at a ratio of 3:1) significant decrease in MAP in eleven patients in propofol group and three patients in ketofol group.

In this study all patients of both groups had increased depth of respiration initially without any change in rate although four patients developed subtle hypoxia in group I and two in group II may be due to over sedation or increased salivation subsided with simple head extension. Persson J et al[12] reported that ketamine induced sympathoadrenal activation may account for improved ventilation.

Mean recovery time in group I patient was significantly better than group II patients in this study which simulate with a study done by Saeed E et al[13] who evaluated three ratios of ketofol infusion (ketamine: propofol 1:1, 1:2, 1:3) for close reduction of distal arm fractures & recommended ketofol 1:2 as an appropriate procedural sedation modalities providing early recovery and shorter hospital stay with minor haemodynamic changes and postoperative side effects.

Adverse events as found in this study were very few and there was no case of hypertension, bradycardia vomiting or laryngospasm in any group. During procedure 80% patients developed insignificant rise of BP from baseline in Group II in comparison to 23.3% patients of Group I. about 33.3% patients of Group II had agitation during recovery period in comparison to 10% as Group I. Higher rate of emergence reaction, postoperative vomiting, compromised airway were found in ketamine monotheraphy specially when used (> 2.5 mg/kg) as found by Green SM et al[(14)] & Strayer et al[(15)]. The suggested explanation is ketamine and propofol complements each other to be more effective clinically while counter acting each other's adverse effects.

Midazolam could be a better alternative than diazepam as it has shorter elimination half- life (2-3 hrs) compared to diazepam (20-50 hrs) which would allow a shorter recovery time in Group II if selected. However, the study was done giving more emphasis on easily available, cheaper and popular drug. It would be more scientific if we could analyze blood gases of all patients and also duration of analgesia. Feedback of patients also not accomplished as most of the procedure was done on outdoor basis.

Conclusion

Combination of ketamine and popofol in bolus (1:1) form provides safer and more effective sedation

and analgesia in PSA than commonly used ketamine and Diazepam combination. Ketofol ensures better haemodynamic stability, procedural success, smooth and early recovery with negligible complications. Ketofol can be a handy option in the armoury of anaesthesiologist for short duration procedures specially in the area of low resources.

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