Original Article

Use of Ketamine-Propofol 'Ketofol' versus Ketamine-Midazolam for Procedural Sedation and Analgesia

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Abstract

Background: *Procedural sedation and analgesia (PSA) is useful technique for unpleasant surgical, diagnostic and interventional procedures while maintaining cardiorespiratory function. Unfortunately, at this time no single agent available that complete PSA successfully, so combinations of different drugs used at varying does to achieve the desired goal.*

Objectives: *The purpose of this study is to observe the effectiveness of combination of ketamine and propofol (Ketofol) in comparison with ketamine midazolam combination in patients undergoing procedural sedation and analgesia (PSA) for short elective and emergency surgeries.*

Methods: *One hundred patient of both sex, ASA grade I & II, age 18 to 50 years were scheduled to undergo different short surgical procedures (less than 1 hour) were randomly assigned into 2 groups. In Group KP (n=50) recieved Ketamine & Propofol (1:1) and Group KM (n=50) received Ketamine and midazolam at the discretion of the anaesthesiologist by using titrated aliquots for completion of the procedure. All perioperative vital parameters, events, complications, recovery status, and cost of sedation regimen were recorded and subsequently analyzed.*

Results: *The two groups were fairly comparable regarding demographic and preoperative data. Group KP remain more stable than Group KM haemodynamicaly; heart rate, systolic blood pressure, diastolic blood pressure and mean blood pressure were significantly higher in Group KM than Group KP during procedure at 5, 10, 15, 20 and 25 minutes (p<0.01). Recovery time was 19.71±7.58 (mean±SD) minutes in Group KP and 32.25±8.91 (mean±SD) minutes in Group KM which was significantly higher (P<0.01). Cost (taka) of sedation regimen was significantly higher in Group KP than Group KM (P<0.01). Regarding sedition related side effects; incidences of hypertension (systolic BP more than 30% of baseline record) was found 1(2%) in Group KP and 5(10%) was found in Group KM and difference was statistically significant (P<0.01). Other notable side effects were desaturation (SpO_2 less than 93 %), airway misalignment, vomiting and agitation were almost similar and differences between two groups were statistically not significant.*

Conclusion: *Combination of ketamine and propofol ((ketofol) appeared to be a safe and efficacious during procedural sedation and analgesia regarding haemodynamic stability and short recovery period in comparison with ketamine midazolam combination for short surgical procedures.*

Keywords: *Procedural Sedation and Analgesia (PSA) Ketamine, Propofol, Ketofol, Midazolam*

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Introduction

Procedural sedation and analgesia (PSA) 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.[1,2] Minimally invasive, non invasive procedure in operating room and outside the operating room needs both sedation & analgesia for safe and successfully completion of these procedures.

With the introduction of shorter-acting sedatives for sedation and opioids for pain control, specific reversal agents for both opioids and benzodiazepines, and the availability of noninvasive monitoring equipment, procedural sedation and analgesia can now be safely administered in many healthcare settings.[3] Thus, anaesthetic agents in procedural sedation and analgesia should provide smooth and fast induction of anesthesia, adequate analgesia rapid and pleasant recovery, and return to preoperative functional status with optimal post procedure analgesia and minimal side effects.

Various drugs are available and used to provide PSA. A short acting benzodiazepine either alone or in combination with opioid, ketamine, propofol, etomidate can be used for PSA. Among these Ketamine is the single most popular agent used to facilitate painful procedure in adult and children for nearly two decades.[4,5,6] It is a "dissociative" anesthetic that functions by blocking communication between the thalamic and limbic regions of the brain, thereby preventing the brain from processing external stimuli.[7] It provides excellent amnesia and analgesia, and preserves muscle tone maintaining protective airway reflexes and spontaneous respiration. [8,9]

Several studies suggested that combining two anaesthetic drugs ketamine and propofol "Ketofol" when administer together in sedative dose, produces effective sedation and analgesia.[10] Propofol is a very potent anaesthetic without having any analgesic property.[2] Patient can maintain spontaneous respiration, but very large dose or rapid administration can produce cardio-respiratory depression. Propofol is rapidly eliminates from the blood, the elimination half life is about 2.5 hours, so it is the drug of choice for procedures when patient need less hospital stay and early discharge.[11] Ketamine and propofol are physiologically compatible for one hour at 23 degree celsius, when administer together.[10] In sub-anaesthetic blood level, ketamine produces intense analgesia, incidence of emergence phenomenon, nausea, vomiting and cardiovascular stimulation are lower when sedated with Propofol, and allows early and smooth recovery, which may not be present when ketamine used with benzodiazepine.[12,13] If ketamine combined with a benzodiazepine prevents agitation and nightmares.[14] Combination of ketamine with newer short acting benzodiazepine; midazolam is another useful regimen for PSA. Midazolam produces amnesia, sedation and ketamine produces dissociation and intense analgesia.[15]

In this study combination of ketamine-propofol (ketofol) was compared to the combination ketamine-midazolam in patients undergoing procedural sedation and analgesia (PSA) for short elective and emergency surgeries. Haemodynamic variables, side effects of drug regimens, recovery time and cost of both regimens were also compared.

Materials and Methods

This prospective randomized study was conducted in CMH, Dhaka, in one calendar year from July 2012 to June 2013. One hundred patient of both sex, age from18 to 50 years, ASA physical grading I and II were scheduled to undergo different short elective and emergency surgical procedures (less than 1 hour) were included in the study. Procedures more than one hour, neurosurgical procedure, pregnancy, raised intracranial pressure, seizure disorder, anatomic airway abnormalities, severe cardiovascular and respiratory disease, severe psychological problem and known to have previous sensitivity or drug reaction with ketamine, propofol and midazolam were excluded from the study. During pre-anaesthetic assessment, every patient underwent thorough physical examination with ASA classifications. Total anaesthetic procedure was explained to every patient and informed consent was taken. An intravenous channel was established by 18G venous canula to all patients before starting the procedure. A baseline pulse, blood pressure, respiratory rate, ECG and SpO_2 were recorded. Patents were randomly distributed in two groups of 50 each. In Group KP patients received ketofol was prepared as a 1:1 mixture of ketamine 10 mg/ml and propofol 10 mg/ml mixed in a 10 ml or 20 ml syringe. Anaesthesia using ketofol was performed by the intravenous administration of 1 to 3 ml aliquots titrated at the discretion of the anaesthesiologist. Group KM patients received midazolam 0.1mg/kg body weight intravenously prior to surgical procedure. Intravenous ketamine was administered 2mg/kg body weight slowly titrated at the discretion of the anaesthesiologist to complete the procedure. Assessment of level of sedation was monitored by using Ramsay Sedation Scale (RSS). [16] The drugs for both groups were

administered slowly in aliquots till RSS reached 5. Surgery was performed when patients did not respond to surgical stimuli in both groups. RSS was maintained level 5 by giving increments in both groups. Patient's vital parameters (heart rate, BP, respiratory rate, Spo2 and ECG) were monitored at 5 minutes interval through out the procedure.

At the end of procedure all patients from both groups were shifted to the recovery room, Recovery status will be assessed by Aldrete Recovery Score.[17] Patients will be considered to be ready to discharge from recovery room when they had stable vital signs, oriented, have no intractable nausea or vomiting have minimum pain, and Aldrete Recovery Score is persistently at least 8 or more than 8. Recovery time was calculated as the time from the last dose of medication given until discharge criteria were met.

Any serious adverse events as well as side effects like desaturation (SpO_2 less than 93%), misalignment of airway, hypertension (systolic BP more than 30% of baseline record), hypotension (systolic BP less than 90 mm of Hg), arrhythmia, vomiting and agitation were observed, recorded and managed in whole perioperative period.

All results were expressed in mean + SD or percentage as applicable. Statistical analyses were carried out using Statistical Package for Social Science (SPSS) for Windows Version 17.0. Results were considered statistically significant if P value less than 0.05.

Results

The demographic and preanaesthtic data were shown in table I. Two groups were similar and fairly comparable with respect to age, body weight, sex, ASA physical status airway assessment and co-morbid conditions and differences were statistically not significant. Various surgical procedures were shown in table II. There were predominance of gynaecological and orthopedic procedures on both groups like dilatation and curettage (D&C), close reduction of fractured bone and dislocated joints. There were no significant differences regarding types of surgery in both groups. All the procedures were done successfully in both groups. Changes in heart rate were shown in table III. Mean of heart rate of Group KM remained significantly higher than Group KP during procedure at 5, 10, 15, 20 and 25 minutes. Change in systolic blood pressure (SBP) between two groups has been shown in Table IV. Mean systolic blood pressure of Group KM remained significantly higher than Group KP during procedure at 5, 10, 15, 20 and 25 minutes. Change

Table I *Patients demographics and preanaesthetic data*

Characteristics	Group KP (n=50)	Group KM (n=50)	P Value	Result
Age in years	36.17±9.23	34.78±8.83	0.58	NS(student 't' test, unpaired)
Sex				
Male	22(44%)	20(40%)	0.81	NS(chi square test)
Female	28(56%)	30(60%)	0.79	NS(chi square test)
Body weight in kg	62.34±7.31	59.54±9.19	0.91	NS(student 't' test , unpaired)
ASA physical status				
ASA grading I	40(80%)	41(82%)	0.95	NS(chi square test)
ASA grading II	10(20%)	9(18%)	0.96	NS(chi square test)
Airway assessment				
Malampatti class I	37(74%)	39(78%)	0.87	NS(chi square test)
Malampatti class II	13(26%)	11(22%)	0.79	NS(chi square test)
Co-morbidity				
Diabetes	4(8%)	3(6%)	0.63	NS(chi square test)
Hypertension	3(6%)	2(4%)	0.58	NS(chi square test)
Asthma	2(4%)	2(4%)	-	NS(chi square test)
Renal disease	-	1(2%)	-	NS(chi square test)
Hypothyroidism	1(2%)	1(2%)	-	NS(chi square test)

Values are expressed in Mean + SD and percentage
NS– Not significant

in diastolic blood pressure (DBP) between two groups has been shown in Table V. Mean systolic blood pressure of Group KM remained significantly higher than Group KP during procedure at 5, 10, 15, 20 and 25 minutes. Change in mean blood pressure (MBP) between two groups has been shown in Table VI. Mean systolic blood pressure of Group KM remained significantly higher than Group KP during procedure at 5, 10, 15, 20 and 25 minutes. Anaesthesia related data were shown in table VII. Procedure times of two groups were almost similar and difference was statistically not significant. Recovery time was 19.71±7.58 minutes in Group KP and 32.25±8.91 minutes in Group KM which was significantly higher. Costs of both sedation regimens were calculated. It was 132.76±10.15 (mean±SD) taka in group KP and 82.85±8.69 (mean±SD) taka in Group KM. Cost was higher in Group KP than Group KM and difference was statistically significant.

Complications or side effects of both sedation regimens were shown in table VIII. Incidences of hypertension (systolic BP more than 30% of baseline record) was found 1(2%) in Group KP and 5(10%) was found in Group KM and difference was statistically significant. Other notable side effects were desaturation (SpO_2 less than 93 %), airway misalignment, vomiting and agitation. Incidences were almost similar and differences between two groups were statistically not significant.

Table II *Types of surgical procedures*

Surgical procedure	Group KP(n=50)	Group KM(n=50)	P Value	Result
D&C	19(38%)	17(34%)	0.48	NS(chi square test)
Incision and drainage of abscess	10(20%)	12(24%)	0.65	NS(chi square test)
Repair of cut injuries and lacerations	8(16%)	10(20%)	0.71	NS(chi square test)
Close reduction of fractures	7(14%)	6(12%)	0.86	NS(chi square test)
Excision and biopsy	4(8%)	3(6%)	0.74	NS(chi square test)
Close reduction of joint dislocation	2(4%)	2(4%)	-	NS(chi square test)

Values are expressed in percentage
NS– Not significant

Table III *Comparison of changes in heart rate (rate/min)*

Time	Group KP(n=50)	Group KM(n=50)	P Value	Result
Pre induction	76.32+5.11	72.87+7.31	0.181	NS(student 't' test , unpaired)
After induction	81.31+4.45	87.53+5.51	0.098	NS(student 't' test , unpaired)
5 minutes	85.31+4.78	116.55+7.11	<0.01	Sig(student 't' test , unpaired)
10 minutes	88.52+5.07	119.09+6.14	<0.01	Sig(student 't' test , unpaired)
15 minutes	91.95+5,54	120.13+6.31	<0.01	Sig(student 't' test , unpaired)
20 minutes	88.14+6.76	113.31+5.23	0.021	Sig(student 't' test , unpaired)
25 minutes	82.78+5.57	101.96+6.09	0.043	Sig(student 't' test , unpaired)
30 minutes	79.79+6.21	88.77+5.63	0.078	NS(student 't' test , unpaired)

Values are expressed in Mean + SD
NS-Not significant
Sig-Significant

Table IV *Comparison of changes in systolic blood pressure (mm of Hg)*

Time	Group KP(n=50)	Group KM(n=50)	P Value	Result
Pre induction	116.76+6.33	118.13+5.61	0.681	NS(student 't' test , unpaired)
After induction	115.89+13.11	127.41+8.14	0.013	Sig(student 't' test , unpaired)
5 minutes	116.18+8.24	141.09+10.43	<0.01	Sig(student 't' test , unpaired)
10 minutes	118.52+8.56	142.65+11.32	<0.01	Sig(student 't' test , unpaired)
15 minutes	117.87+7.09	138.83+10.41	<0.01	Sig(student 't' test , unpaired)
20 minutes	115.89+7.53	132.76+9.11	0.019	Sig(student 't' test , unpaired)
25 minutes	116.09+6.24	126.87+9.01	0.045	Sig(student 't' test , unpaired)
30 minutes	117.33+7.65	122.09+10.41	0.72	NS(student 't' test , unpaired)

Values are expressed in Mean + SD
NS-Not significant
Sig-Significant

Table V *Comparison of changes in diastolic blood pressure (mm of Hg)*

Time	Group KP(n=50)	Group KM(n=50)	P Value	Result
Pre induction	76.53+7.04	74.39+6.32	0.171	NS(student 't' test , unpaired)
After induction	74.90+5.63	80.21+6.98	0.041	Sig(student 't' test , unpaired)
5 minutes	76.29+4.02	86.23+6.46	<0.01	Sig(student 't' test , unpaired)
10 minutes	75.88+7.10	87.68+6.87	<0.01	Sig(student 't' test , unpaired)
15 minutes	77.34+6.19	85.98+5.79	<0.01	Sig(student 't' test , unpaired)
20 minutes	76.37+7.10	82.09+6.98	0.023	Sig(student 't' test , unpaired)
25 minutes	75.78+6.33	81.76+6.65	0.038	Sig(student 't' test , unpaired)

Table V *Comparison of changes in diastolic blood pressure (mm of Hg)*

Time	Group KP (n=50)	Group KM(n=50)	P Value	Result
Pre induction	76.53+7.04	74.39+6.32	0.171	NS(student 't' test , unpaired)
After induction	74.90+5.63	80.21+6.98	0.041	Sig(student 't' test , unpaired)
5 minutes	76.29+4.02	86.23+6.46	<0.01	Sig(student 't' test , unpaired)
10 minutes	75.88+7.10	87.68+6.87	<0.01	Sig(student 't' test , unpaired)
15 minutes	77.34+6.19	85.98+5.79	<0.01	Sig(student 't' test , unpaired)
20 minutes	76.37+7.10	82.09+6.98	0.023	Sig(student 't' test , unpaired)
25 minutes	75.78+6.33	81.76+6.65	0.038	Sig(student 't' test , unpaired)
30 minutes	75.08+5.83	77.23+6.11	0.62	NS(student 't' test , unpaired)

Values are expressed in Mean + SD
NS-Not significant
Sig-Significant

Table VI *Comparison of changes in Mean blood pressure (mm of Hg)*

Time	Group KP (n=50)	Group KM (n=50)	P Value	Result
Pre induction	90.66+7.19	89.31+6.23	0.671	NS(student 't' test , unpaired)
After induction	91.60+5.21	97.91+6.78	0.041	Sig(student 't' test , unpaired)
5 minutes	91.34+4.75	101.14+6.08	<0.01	Sig(student 't' test , unpaired)
10 minutes	92.68+7.60	103.88+6.45	<0.01	Sig(student 't' test , unpaired)
15 minutes	91.56+6.29	102.87+5.06	<0.01	Sig(student 't' test , unpaired)
20 minutes	91.48+7.19	97.95+7.01	0.027	Sig(student 't' test , unpaired)
25 minutes	89.47+6.72	94.31+6.49	0.041	Sig(student 't' test , unpaired)
30 minutes	89.97+5.76	92.18+6.42	0.76	NS(student 't' test , unpaired)

Values are expressed in Mean + SD
NS-Not significant
Sig-Significant

Table VII *Anaesthesia related data*

Variables	Group KP(n=50)	Group KM(n=50)	P Value	Result
Procedure time (minutes)	21.25 ± 8.57	20.83 ± 9.78	0.791	NS(student 't' test , unpaired)
Recovery time (minutes)	19.71±7.58	32.25±8.91	<0.01	Sig(student 't' test , unpaired)
Cost of sedation (taka)	132.76±10.15	82.85±8.69	<0.01	Sig(student 't' test , unpaired

Values are expressed in Mean + SD
NS-Not significant
Sig-Significant

Table VIII *Complications of sedation*

Complication	Group KP (n=50)	Group KM (n=50)	P Value	Result
Desaturation	2(4%)	3(6%)	0.781	NS(chi square test)
Airway misalignment	2(4%)	2(4%)	-	NS(chi square test)
Hypertension	1(2%)	5(10%)	0.012	Sig(chi square test)
Vomiting	1(2%)	1(2%)	-	NS(chi square test)
Agitation	5(10%)	4(8%)	0.832	NS(chi square test)

Values are expressed in percentage
NS-Not significant
Sig-Significant

Table IX *Ramsay Sedation Scale*

If Awake
1-Anxious, agitated, restless
2-Cooperative, oriented, tranquil
3-Responsive to commands only
If Asleep
4-Brisk response to light glabellar tap or loud auditory stimulus
5-Sluggish response to light glabellar tap or loud auditory stimulus
6-No response to light glabellar tap or loud auditory stimulus

Table X *Aldrete Recovery Score*

Parameter	Number
Activity	
Voluntary movement of all limbs to command	2
Voluntary movement of two extremities to command	1
Unable to move	0
Respiration	
Breathe deeply and cough	2
Dyspnea, hypoventilation	1
Apneic	0
Circulation	
BP +/- 20 mm Hg of pre-anaesthesia level	2
BP > 20-50 mm Hg of pre-anaesthesia level	1
BP > 50 mm Hg of pre-anesthesia level	0
Consciousness	
Fully awake	2
Arousable	1
Unresponsive	0
Colour	
Pink	2
Pale, blotch	1
Cyanotic	0

Total score must be > 8 at conclusion of monitoring.

Discussion

The goals of PSA are to provide an adequate level of sedation while minimizing pain and anxiety, maximizing amnesia, minimizing the potential for adverse drug related events, and maintaining a stable cardiovascular and respiratory status.[18] Unfortunately, the ideal pharmacotherapeutic agent has not been found; however, a number of medications provide some of these properties. Traditionally midazolam, propofol, or etomidate has been used as the primary agent to facilitate PSA in emergency department.[19-21] In practice of emergency medicine, ketamine possesses several alluring pharmacologic characteristics for use during PSA.[22,23] The use of propofol and ketamine as single agents for procedural sedation and analgesia has grown in popularity.[24] In this present study, we compared combination of ketamine-propofol (keofol) with ketamine-midazolam for procedural sedation and analgesia in different short surgical procedures.

Regarding haemodynamic parameters of patients between two groups; heart rate, systolic, diastolic and mean blood pressures were observed more stable in patients with ketofol. During procedure, heart rate, systolic blood pressure, diastolic blood pressure and mean blood pressure found to remain significantly high with ketamine-midazolam than with ketofol.

Arora et al[25] studied ten adult patients over age 18 for procedural sedation analgesia given by Ketofol in 1:1 ratio and proved the haemodynamic stability of this mixture of ketamine-propofol. Akin et al[26] showed in a study that the combination of low dose ketamine with propofol preserved mean arterial pressure without prolonging recovery or increasing the incidence of adverse effects. This study was also consistent with the result of Hui et al[27] who found stable cardiovascular stability when using different mixture of propofol and ketamine in comparison to either drugs using solely. These haemodynamic findings of the present study found similar to a study conducted by Hernandez et al.[28] They compared three techniques for intravenous anaesthesia (ketamine-midazolam, ketamine-propofol and propofol-fentanyl). They found that ketamine-propofol had most stable haemodynamics, ketamine-midazolam had higher number of hypertensive peaks. The haemodynamic stability of ketofol may be because of sympathomimetic actions of ketamine were effective in counteracting the haemodynamic depression of Propofol[27, 29]

Short recovery time is a valuable attribute of procedural sedation and analgesia. The mean recovery time was 19.71±7.58 (mean±SD) minute in Group KP with ketofol is comparable to that of other procedural sedation and analgesia regimen noted for their rapid recovery times. Studies of propofol sedation report mean recovery times from 15 ±11 minutes to 23 ±11 minutes.[30,31] Mean recovery times ranging from 25 to 58 minutes have been reported when intravenous ketamine is used alone.[32,33] In this study recovery time for Group KM with ketamine-midazolam was 32.25±8.91 (mean±SD) minutes, which was significantly longer than ketofol in Group KP. In a trial of 40 adult patients undergoing endometrial biopsy, by Akin et

al[34] reported that the combination of propofol (1mg/kg) and fentanyl (1 microgram/kg) was compared to the combination of propofol and ketamine (2:1); the time of recovery was similar in both the groups. Sharief et al[35] used 1mg/kg of propofol and 0.5mg/kg of ketamine in pediatric sedation and analgesia for closed reduction of forearm fractures and found effective sedation with rapid recovery no reported case of apnea or haemodynamic compromise. A more recent evaluation of three ratios of ketofol infusions (ketamine: propofol; 1:1, 1:2 and 1:3) for close reduction of distal forearm fractures, recommended ketofol 1:2 as an appropriate procedural sedation modalities providing early recovery and minor haemodynamic changes.[36]

Sedation related complications like desaturation (SpO_2 less than 93%), misalignment of airway, vomiting during recovery and agitation were observed and recorded within two groups. Numbers of these events were few and fairly comparable. Transient hypertension (systolic BP more than 30% of baseline record) was found significantly higher with ketamine-midazolum than ketofol. Studies suggested that the minimal change observed in arterial pressure with ketofol than ketamine-midazolam may be because sympathomimetic actions of ketamine were effective in counteracting the haemodynamic depression of propofol.[27, 29] There were no serious adverse events reported in any patient.

The total cost of sedation was 132.76±10.15 (mean±SD) taka in Group KP and 82.85±8.69 (mean±SD) taka in Group KM respectively and difference is significantly higher with ketofol.

Limitations of the study were small sample size and not being able to measure end tidal carbon di oxide ($ETCO_2$) during procedure due to unavailability of that facility in spontaneously ventilated patients.

Conclusion

Combination of ketamine-propofol (ketofol) in bolus form provides safer sedation in PSA with stability of vital signs, swift recovery with minimum complication. Ketamine-midazolam combination was associated with increase in both heart rate and blood pressure during procedure as well as longer recovery period. Ketofol was associated with swift recovery and only a few untoward side effects. In conclusion ketofol appeared to be a safe and efficacious during procedural sedation and analgesia for short surgical procedures.

References

1. ACEP, Clinical policy: Procedural Sedation and Analgesia in the Emergency Department. Annal of Emergency Medicine 2005 February; 42(2):177-196.
2. Aouad M, Moussa A, Dagher C. Addition of Ketamine to propofol for Initiation of Procedural Anaesthesia in Children Reduces propofol consumption and Preserves Haemodynamic Stability. Acta Anaesthesiol Scand 2008; 52(4):561-565.
3. Continuum of depth of sedation definition of general anesthesia and levels of sedation/analgesia. American Society of Anesthesiologists. Available from: http://wwwasahqorg/publicationsAndServices/standards/20pdf. [cited on 2004 Oct 27], [accessed on 2012 Jun 27]
4. Daabis M, Elsherbiny M, Alotibi R. Assessment of different concentration of Ketofol in procedural operaton. BJMP March 2009; 2(1): 27-31.
5. Green SM, Roback MG, Krauss B, et al. Predictors of Airway and Respiratory Adverse Events with Ketamine Sedation in Emergency Department: an Individual Patient Data Meta Analysis of 8,282 Children. Annals of Emergency Medicine 2009; 54:158-168.
6. Green SM, Rothrock SG, Lynch EI, et al. Intra muscular ketamine sedation in the emergency department; Safety profile in 10222 cases. Ann Emerg Med 1998; 31:688-97.
7. Green SM, Krauss B. The semantics of ketamine [editorial]. Ann Emerg Med. 2000; 39:480-482.
8. Krauss B, Green SM. Procedural sedation and analgesia in children. Lancet. 2006; 367:766-780.
9. Warncke T, Stubhaug A, et al. Ketamine, an NMDA receptor antagonist, suppresses spatial and temporal properties of burn-induced secondary hyperalgesia in man: a double-blind, cross-over comparison with morphine or placebo. Pain. 1997; 72:99-106.

10. Trissel L.A., Gilbert D.L., Martinez J.F, Compatibility of Propofol Injectable Emulsion with Selected Drugs During Simulated Y-Sight Administration, Am J H Syst Pharm 1997; 54: 1281-92.

11. Aitkenhead A.R., Robwbotham D.J., Smith G., Textbook of Anaesthesia, 4th ed. UK. Churchill Livingstone 2001; (4):175-176.

12. Ann W., Emergency Medicine 2007; Felfering Journal of Royal Naval Medical Service, 2006; White International Anaesthesia Clinics, 2008.

13. William E.V.. Andolfetto G., Prospective Evaluations of "Ketofol" (Ketamine/Propofol Combination) for Procedural Sedation and Analgesia in the Emergency Department, Annal of Emergency Medicine 2007 January; 49(1):23-30. Epub 2006 October 23.

14. Green SM, Johnson NE. Ketamine sedation for pediatric procedures; Part 2, review and implications. Ann Emerg Med 1990; 19:1033-46

15. Edward Morgan, Maged S. Mikhail, Michail J. Murray. Clinical Anaesthesiology. 4th ed. USA. McGraw-Hill, 2006: 179-203.

16. Griffith RD, Jones C. Recovery from Intensive Care. British Medical Journal 1999; 319: 427-429.

17. Aldrete, J.A. The post anesthetic recovery score revisited. J Clin Anesth. 1995;13:89–91.

18. Nelson D. Procedural sedation in the emergency department. In: Krauss B, Brustowicz RM, editors. Pediatric and Procedural Sedation and Analgesia. Baltimore: Lippincott Williams and Wilkins; 1999;161.

19. Godwin SA, Caro DA, Wolf SJ, et al. Clinical policy: procedural sedation and analgesia in the emergency department. Ann Emerg Med 2005;45:177-196.

20. Bahn EL, Holt KR. Procedural sedation and analgesia: a review and new concepts. Emerg Med Clin North Am 2005;23:503-517.

21. Baker SN, Weant KA. Procedural sedation and analgesia in the emergency department. J Pharm Pract 2011;24:189-195.

22. Cromhout A. Ketamine: its use in the emergency department. Emerg Med 2003;15:155-159.

23. Newton A, Fitton L. Intravenous ketamine for adult procedural sedation in the emergency department: a prospective cohort study. Br Med J 2008; 25:498-501.

24. Green SM. Research advances in procedural sedation and analgesia. Ann Emerg Med. 2007;49:31–36

25. Arora S, martin CL, Fernandez MM, Wagner JG, Herbert M. Combining Ketamine and Propofol (Ketofol) for emergency sedation in emergency department. Annal of Emergency Medicine 2007; 50(3): 121.

26. Akin A, Esmaoglu A, Guler G, Demercioglu R, Narin N, Boyaci A. Propofol and Propofol Ketamine in paediatric patient undergoing cardiac catheterization. Pediatr Cardiol 2005; 26(5): 553-557.

27. Hui TW, Short TG, Hong w, Suen T, Gin T, Plummer J. Additive interactions between Propofol and Ketamine when used for anaesthesia induction in female patients. Eur J Anaesthesiology 1995; 82: 641-648.

28. Hernandez C, Parcamon F, Garcia-Velasco P, Velaplana J, Garcia C, Villalong A. Comparative study of three techniques for total intravenous anaesthesia: midazolam ketamine, propofol-ketamine and propofol-fentanyl. Rev Esp Anestesiol Reanim 1999 April; 46(4): 154-158.

29. Furuya A, Matsukawa T, Czaki M, Nishyama T, Kume M, Kumazawa T. Intravenous Ketamine attenuates arterial pressure changes during induction of anaesthesia with Propofol. Eur J Anaesthesiology 2001; 18: 88-92.

30. Havel CJ, Strait RT, Hennes H. A clinical trial of Propofol versus midazolam for procedural sedation in a paediatric emergency department. Acad Emerg Med. 1999; 6: 989-997.

31. Vardi A, SalemY, Padesh S. Is Propofol safe for procedural sedation in children? A prospective evaluation of Propofol versus Ketamine in paediatric critical care. Crit Care Med 2002; 30: 1231-1236.

32. Dachs RJ, Innes GM. Inravenous sedation of paediatric patients in emergency department. Ann Emerg Med 1997; 29: 146-150.

33. Wathen JE, Roback MG, et al. Does midazolam alter the clinical effects of intravenous Ketamine sedation in children? A double blinded, randomized, controlled, emergency department trial. Ann Emerg Med 2000. 36: 579-588.

34. Akin A, Guler G, Esmaoglu A, Bedirli N, Boyaci. A comparison of fentanyl-propofol with Ketamine-propofol combination for sedation during endometrial biopsy. J Clin Anaesth, May 2005;17(3): 187-190.

35. Sharrief GQ, Trocinski DR, Kanegaye JT, Fisher B, Harley JR. Ketamine Propofol combination sedation for fracture reduction in the paediatric emergency department. Pediatr Emerg Care 2007; 23(12): 881-884.

36. Saeed E. Ketofol infusion as a procedural sedation and analgesia for minor orthopaedic surgeries: evaluation of dose- outcome relation. Ain Shams Journal of Anaesthesiology 2011; 4(1): 63-74.