Original Paper

EVALUATION OF KETOFOL (KETAMINE PROPOFOL COMBINATION) AS TOTAL INTRAVENOUS ANAESTHETIC FOR BURN DRESSING IN ADULT PATIENT

Samad MA[1], Islam MS[2], Ahmed M[3], Maruf AA[4]

Abstract

Introduction: **Pain management during burn dressing changes is a critical part of treatment in acute burn injuries.**

Objective: **This study was carried out with objective of finding out an ideal analgesic, sedative and/or anxiolytic combination that would serve the purpose as well as minimize the unwanted effects of traditionally used ketamine.**

Methods: **A total of 28 patients with burns of 15-50% of total body surface area were included in this study. Each patient received Propofol and Ketamine 1mg/kg body weight as induction dose and Ketamine 1mg/kg/hour and Propofol 4mg/kg/hour as maintenance dose till procedure ends. All perioperative vital parameters, events and complications were recorded and subsequently analyzed.**

Results: **Mean age of the patients was 31±6.49 years while mean duration of the surgery was 34±9.42 minutes. Mean induction time was 24±5.13 seconds. Heart rate (H/R), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were increased during the procedure, but were within acceptable limit. Five patients had raised H/R and two had raised SBP 20% above their baseline level for transient period which came to normal level without any active management. All patients maintained adequate oxygenation throughout the procedure. There was no incidence of apnoea or hypoventilation or vomiting. One patient had mild form of emergence delirium. Mean recovery time from anaesthesia was 52±8.17 minutes while time gap for further analgesic requirement after surgery was 126±11.46 minutes.**

Conclusion: **Ketamine and Propofol combination (Ketofol) for procedural sedation and analgesia is effective and appears to be safe for minor but extremely painful procedures like burn dressing. Few subtle adverse events occurred and were self limited or responded to minimal interventions.**

Keywords: **Ketofol, sedation, analgesia, burn dressing**

Introduction

Burn pain induces one of the most severe from of acute pain[1]. Burn dressing changes require profound analgesia for a short duration and opioid administration is the main-stay of procedure related pain management in patients with burn[1,2]. General anaesthesia for repeated dressing changes improves patient comfort and reduces background analgesic demand. The combination of potent analgesic ketamine and profound sedative propofol (Ketofol) for minor but extremely painful procedure like burn dressing theoretically may be beneficial with the rationale of being that using lower doses of each agent may result in reduction of the undesirable adverse effects of both agents while maintaining optimal conditions for performing procedures[3]. This study was carried out to find out the efficacy and safety of combination of ketamine and propofol as anaesthetic in patients undergoing burn dressing.

1. Lt Col Md Abdus Samad MBBS, MCPS, FCPS, Department of Anaesthesia and Intensive Care, CMH, Dhaka; 2. Brig Gen Md Saiful Islam MBBS, MCPS, FCPS, Professor and Head, Department of Anaesthesia, AFMC; 3. Lt Col Masud Ahmed MBBS, FCPS, CMH, Dhaka; 4. Lt Col Md Abdullah Al Maruf MBBS, FCPS, CMH, Dhaka.

Materials and Methods

This prospective study was carried out in Bangladesh Naval Ship Patenga Hospital and Combined Military Hospital (CMH), Dhaka during the period of Nov'2007 to Jul' 2011 on 28 burn patients who required elective dressing change in operation theatre. No patient was considered twice in the study.

Inclusion criteria

- Age within the range of 18 to 60 years
- ASA physical status of patient was grade I and II
- Percentage of burn within the range of 15 to 50%

Exclusion criteria

- Patients with haemodynamic instability, electrolyte imbalance, impaired hepatic & renal function and psychologically unstable
- Patients having signs of raised intracranial pressure, history of epilepsy, ischemic heart disease
- History of allergy to any of the drugs used
- Unwilling to undergo study

Following local ethics committee approval, informed written consent was obtained from each patient. Preanaesthetic checkup carried out thoroughly 24 hours before procedure and all were premedicated with Tablet Bromazepam 03 mg at bed time on day before operation. Study subjects were in routine preoperative fasting of 6 hours and during the procedure all were infused with Hartmann's solution at the rate of 2.5 ml/kg/hour. On operation date vital parameters (heart rate, systolic and diastolic blood pressure, respiration rate, oxygen saturation and electrocardiogram) were monitored and recorded in the following sequences-

- t0 - baseline (just before induction)
- t1 - 05 minutes after induction
- t2 - 15 minutes after induction
- t3 - 30 minutes after induction
- t4 - 45 minutes after induction
- t5 - 60 minutes after induction

All patients were induced by Injection Ketamine 1mg/kg and Injection Propofol 1mg/kg and anaesthesia was maintained by drip of Ketamine 1mg/kg/hour and Propofol 4mg/kg/hour mixed with normal saline, using infusion pump. Intraoperative stresses manifested by lacrimation, sweating, limb movement were noted. The induction time (interval between induction dose and abolishment of eyelash reflex) was also recorded in each patient. Recovery (Score >7) from anaesthesia was assessed by Post Anaesthesia Aldrete-Kronlik score[4] in the recovery room or postoperative ward. Visual Analogue Scale (VAS) score (0-10) were assessed after complete recovery. Analgesics (Injection pethidine 0.5 mg/kg) were administered when Vas score was >5 and the time gap from induction to analgesic requirement was noted for each patient. Throughout this period each patient was observed for any other complications like apnoea or hypoventilation (rate $\leqslant$ 8/min) desaturation (SpO2 $\leqslant$ 90%), shivering, vomiting, emergence delirium (manifested by excitement, confusion, fear, euphoria etc). Complications were managed accordingly. Postoperative questionnaire were carried out on the next day of procedure. All data were collected in a preformed data sheet and subsequently analyzed using statistical package of social science (SPSS). Results were expressed as mean±SD and categorical data were expressed in percentage (%) and frequency (f).

Results

Mean age of the patient was 31 ± 6.49 years. Mean percentage of surface area burnt was 24+4.37% (Table-I). Haemodynamic parameters (heart rate, SBP, DBP) all increased during the procedures but within acceptable level. Electrocardiogram showed sinus rhythm in all patients. Respiratory parameters (respiration rate & oxygen saturation) were very stable during the procedure (Table-II). One patient showed signs of inadequate anaesthesia in the form of lacrimation and sweating (Table III). Five patients had clinically insignificant tachycardia and two had raised systol BP (>20% of baseline level) which came to normal level within few min without any active management. No patient had vomiting or developed hypoventilation (respiration rate < 28/min) or apnoea during or after the procedure. One patient had minor delirium without agitation which continued for about 10 min after the procedure (Table IV). Mean induction time required with bolus Ketofol was 24±5.13 sec and recovery time was 52±8.17 min. Mean time required for further analgesic demand by the patient was 126±11.46 min (Table V).

Table -I: Patient criteria (n=28)

Variables	Unit	Findings
Mean age	years	31 ± 6.49
Sex (M/F)	Frequency	13/15
Mean body weight	Kilogram (kg)	56.7 ± 8.84
ASA Grade (I/II)	Frequency	23/05
Mean Burnt Area	Percentage	24 ± 4.37

Table -II: Preoperative Vital parameters (n=28)

Time	Heart rate in min	SBP mm of Hg	DBP mm of Hg	Respiration rate in min	SpO2 (%)	ECG
t0	86±8.92	114±12.41	68±9.14	16±2.14	98±0.82	SR
t1	94±6.31	122±10.67	76±8.75	18±3.52	99±0.34	SR
t2	96±7.64	124±9.18	77±7.28	18±4.17	98±1.28	SR
t3	94±8.14	121±8.31	76±6.64	16±5.42	98±1.75	SR
t4	91±6.57	116±7.16	72±6.92	16±3.77	99±0.16	SR

Table -III: Indicators / Signs of inadequate anaesthesia (n=28)

Signs / Indicators	f
Lacrimation	01
Sweating	01
Limb movement	-
Unsatisfied anaesthetic technique	01

Table -IV: Anaesthetic Complications (n=28)

Complications	f
Tachyarrhythmia	05
Hypertension	02
Vomiting	0
Delirium	01
Apnoea/ hypoventilation	0
Inadequate anaesthesia	01

Table -V: Other important findings (n=28)

Variables	Unit	Findings
Mean Induction time	Second	24±5.13
Mean duration of procedure	Minute	34 ± 09.42
Mean recovery time (Score > 8)	Minute	52 ± 8.17
Mean time for further analgesic requirement (VAS >5)	Minute	126±11.46

Discussion

Pain management is a critical part of treatment in acute burns which often remains untreated[5]. Following the initial resuscitation of burn patients, the pain experienced may be divided into a "background" pain and 'break through' pain associated with painful procedures as dressing changes[5]. Untreated pain and improper sedation may result in psychological distress such as post traumatic stress disorder, major depression or delirium. As one of the main drugs, ketamine (phencyclidine derivatives) can be used both in primary and secondary hyperalgesia, it also alleviates wind up pain. This effect is unique to Ketamine and is due to reduction of hyperexcitability through the NMDA receptor. More-over it has shown to attenuate the development of acute tolerance to opioids[6].

Propofol (2, 6 diisopropylphenol) is a lipid soluble sedative agent with little or no analgesic potential. Both Ketamine and Propofol as individual agent have gained popularity for procedural sedation and analgesia. But the unwanted effects of each drug alone have limited their adoption in selected population. This study represents a novel application of the combination of two well known medications whose characteristics appear to be complementary. Ketamine produces dose related increase in the rate pressure product and a transient increase in cardiac index; both peripheral resistance and heart rate are augmented along with its widely known emergence phenomenon and emetic effect.

But Propofol balances the negative effects of Ketamine by its cardiodepressant and antimetic effects. At the same time respiratory depressant effect of propofol is also attenuated by Ketamine[7]. So using combination of Ketamine and Propofol (Ketofol) allows analgesia and sedation to be achieved with lower total doses of each drug resulting in favourable adverse event and recovery profile[8].

Till to date variable miligram to miligram ratio of Propofol and Ketamine were used ranging from (10:1 - 1:1) even in a single syringe offering a simple practical approach to medication preparation and use; yet the optimum dose of these agents in combination is unclear[3,8]. In our study we have used bolus induction dose of Propofol and Ketamine in 1:1 ratio and maintenance drip of both in standard dosages. To counteract the demerits of Ketamine, like emergence delirium, vomiting and sympathomimetic effect several other

combinations, like Ketamine-Midazolum, Ketamine-Fentanyl, Ketamine-Dexmeditomidine have been used with more or less success[6,9,10]. Ketamine reduces propofol injection pain by attenuating the afferent pain pathway[11].

The advantages of Ketamine in terms of better haemodynamics intraoperatively when combined with propofol as observed in our study is supported by other studies too[12, 13]. Hernandez et al compared three techniques for intravenous anaesthesia (Midazolam- Ketamine, Propofol-Ketamine and Propofol- Fentanyl). They found that Propofol- Ketamine had most stable haemodynamics. Midazolam- Ketamine had higher number of hypertensive peaks[14]. In our study we continued both Propofol and Ketamine drips and the change of haemodynamics were clinically insignificant. The major advantage of Ketamine is that it usually preserves airway patency and respirotory function[15] as also observed in our study there was no single case of apnoea, hypoventilation or even desaturation which is not uncommon when propofol used alone[12] or in combination with fentanyl[14]. The most frequently mentioned adverse effect of Ketamine is emergence reaction or hallucination and the incidence varies from 9% to 50% patients[15]. Rosendo Mortero F. et al found a significant reduction in the incidence of emergence delirium when propofol and Ketamine were used in combination to Ketamine alone[16], but can't totally abolish it as also found in our study (1 in 28 cases).

In our study there was no single case of per or postoperative vomiting.Green et al found that emesis occurring after Ketamine administration modestly associated with increasing age and higher incident in those patients older than five years of age (12.1%) compared with younger patients (3.5%) which can be reduced by combining it with propofol[17].

Mean Recovery time from Ketofol in our study was 52 + 8.17 min and it significantly reduced requirement of postoperative analgesic as detected by VAS score. Mean time required for further analgesic requirement was 126+11.46 mins. It would be better if we could assess the depth of anaesthesia by Bispectral Index (BIS), the facility for which we don't have. Instead we used clinical parameters which detected one in 28 patients with inadequate anaestheisa who subsequently expressed his dissatisfaction with the anaesthetic technique.

The primary limitations of our study were small sample size, the lack of double blind configuration and the large number of end points in relation to sample size.

Further research with larger samples comparing Ketofol to other common procedural sedation and analgesia could further document safety, efficacy of Ketamine and Propofol combination for minor surgical procedure in operating room or for procedural sedation and analgesia outside operating room.

Conclusion

In conclusion burn patients suffer from daily background pain as well as procedural pain. General anaesthesia for burn procedures bring down background pain and analgesic requirement. The combination of Ketemine and propofol in total intravenous anaesthesia for these dressings provides excellent intraoperative conditions, stable haemodynamics and respiratory parameters and prolonged postoperative analgesia with a low incidence of emergence delirium.

References

1. Pal SK, Cortiella J, Herndon D. Adjunctive methods of pain control in burns. Burns 1997; 23: 404-412.

2. Faucher LD. Modern Pain Management in Burn Care. Problems in General Surgery; Volume- 20. Philadelphia: Lippincott Williams & Wilkins Inc; 2003.p.

3. Slavic VC, Zed PJ. Combination of Ketamine and Propofol. Pharmacotherapy 2007 November ;27 (11): 1588-98.

4. Aldrete JA. The postaneasthetic recovery score revisited. J Clin Anaesth 1995; 7:89-91.

5. Summer GJ, Puntillo KA, Miakowski C, Gren PG, Levine JD. Burn injury pain: the continuing challenge. J Pain 2007;8:533-48.

6. Kissin I, Bright CA, Bradley Jr EL. The effect of ketamine on opioid-induced acute tolerance: can it explain reduction of opioid consumption with ketamine-opioid analgesic combinations?

Anesth Analg 2000; 91: 1483-8.
7. Furuya A, Matsukawa T, Czaki M Intravenous Ketamine Attenuates artierial pressure changes during induction of anaesthesia with propofol. Eur J Anaesthesiol 2001; 18: 88-92.
8. Elaine VW, Gary A. A Prospective evaluation of Ketofol (Ketamine-Propofol Combination) for procedural sedation and analgesia in emergency department. Annals of Emergency Medicine 2007 : 41 (1); 27-30.
9. Scher CS, Gitlin MC. Dexmedetomidine and low-dose ketamine provide adequate sedation for awake fibreoptic intubation. Can J Anesth 2003; 50: 607-10.
10. Irmak A, Oktay C, Cete Y, Akyol C, Kilic C I, Bozdemir N. The effect of midazolam on the side effects of Ketamine used for pediatric sedation in the emergency department. Turkiye Acil Tip Dergisi 2004; 4: 24-33.
11. Tan CH, Onsiong MK, Kua SW. The effect of Ketamine pretreatment on propofol injection pain in 100 women. Anaesthesia 1998; 53: 302-5.
12. Hui TW, Short TG, Hong W, Suen T, Gint, Plummer J. Additive interactions between propofol and ketamine when used for anaesthesia induction in female patients. Anaesthesiology 1995; 82: 641 - 48.
13. Kaushik Saha, Saigopal M, Rajini Sundar, Palaniappan M, Anil C Mathew. Comparative evaluation of propofol-ketamine and propofol-fentanyl in minor surgery. Indian J Anaesth 2001; 45(2): 100-103.
14. 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): 154-8
15. Petrack EM. Ketamine. Clin Ped Emerg Med 2000; 1: 281-284.
16. Rosendo F. Mortero et al. The effects of small-dose ketamine on Propofol sedation: respiration, post-operative mood, perception, cognition and pain. Anaesth Analg 2001; 92: 1465-9.
17. Green SM, Kuppermann N, Rothrock SG et al. Predictors of adverse events with intramuscular ketamine sedation in children. Ann Emerg Med 2000; 35: 35-42.