



Original Research Article

Clinical investigation on the analogy between the ketofol (Amalgamation of Ketamine and Propofol) and ketamine and midazolam for procedural sedation – A single blinded study

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ARTICLE INFO

Article history:

Received 11-11-2019

Accepted 12-11-2019

Available online 28-02-2020

Keywords:

Procedural sedation

Ketofol

ABSTRACT

Introduction and Aims: Decades of research for an ideal sedative agent that could provide both sedation and analgesia with minimal side effects to the patients has failed to find one. Research was then shifted to finding combination of drugs which could suffice the ideal sedative agent. Of these Ketofol showed promising results.

Aim of this study is to “Assess the efficacy and safety of propofol and ketamine amalgamation (ketofol) and comparing the superiority over ketamine and midazolam combination for procedural sedation”.

Materials and Methods: In this prospective randomized single blind study, 50 patients between 15 to 60 years of both males and females, ASA Grade I and Grade II were allocated into two groups. Patients in group 1 received ketofol and group 2 patients received ketamine and midazolam. The comparison between the two groups was done using Two-Sample T-Test, With the help of SPSS version 15.0 Statistical calculator, sample size calculated = 5 to 17, and actual power calculated with this sample size was 0.990 to 0.997 which shows significance of the study.

Results: The study showed statistically significant ($p < 0.005$) difference in HR, DBP, SBP, MBP and recovery time between two groups. Group 1 patients showed stabilized parameters and rapid recovery time than group 2 patients

Conclusion: Ketofol is safe and efficient sedative combination which can be utilized in emergency department, daycare and OT settings with comfort, ease and without any complications. It is close to ideal sedative agent.

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1. Introduction

The management of sedation and analgesia is one of the important components of comprehensive anaesthetic care for patients of all ages and, therefore, a primary concern for the Anaesthesiologist. Because of an array of reasons some of which include the fear of over sedation, concern of altering physical findings, or underestimation of patient needs. Adequate provision of pain control is

not achieved appropriately. Many of the drugs used for sedation and analgesia have the inherent properties to cause central nervous system, respiratory, or cardiac depression. To minimize complications, the appropriate drug(s) and dosages must be chosen, monitored, and administered in the proper setting, and a patient evaluation should be performed before, during, and after their use.

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.” The American College of Emergency

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Physicians (ACEP)¹ defines procedural sedation as "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 cardio respiratory function.

The ideal sedative agent should possess analgesic and amnestic properties, has rapid onset and short duration of action, is safe and allows rapid recovery and discharge, should maintain an effective level of sedation, in absence of hemodynamic or respiratory compromise, and also should lack post procedural side effects. A variety of agents have been studied for procedural sedation, however no currently used agent meets all of these criteria. Alternatively a combination of Drugs has been used to reach the idea I state. There are numerous choices of drugs available that have been used to provide p rocedural Sedation. The success rests in formulating the most appropriate regimen based on the patient demographics and the desired endpoint of the procedural Sedation.

Ketamine and Propofol are two agents that have been well studied and are commonly utilized as single agents for sedation.

Propofol is a non-opioid, non-barbiturate, sedative-hypnotic agent with rapid onset and short duration of action. It possesses anti-nauseate effects and reliably produces sedation. Adverse effects² include dose-related cardiovascular and respiratory depression and bradycardia. Propofol is known to be amnestic but not known to be analgesic, which for some clinicians is a potential concern when performing painful procedures.

Ketamine is a phencyclidine derivative classified as a dissociative sedative and is known to provide analgesia and amnesia. It causes little or no respiratory or cardiovascular depression. However, widespread use of ketamine as a single agent for procedural sedation and analgesia in adults has been limited by the occurrence of emergence phenomena³ and the concern of inducing vomiting or laryngospasm.

Ketamine and propofol administered in combination from separate syringes has been used successfully in a variety of settings, including sedation for spinal anaesthesia, as well as for gynaecologic, ophthalmologic, and cardiovascular procedures in adults and children. This combination has been favoured because of the opposing hemodynamic and respiratory effects of each drug. The use of ketamine in conjunction with propofol has been shown to reduce the dose of propofol required to achieve sedation,⁴ and this combination is believed to result in less toxicity than either drug alone because their complementary effects enable the use of lower doses of each drug.

Administering ketamine and propofol mixed in the same syringe (so-called ketofol) has been shown to be efficacious in the operating room and in ambulatory settings.⁵ ketamine and propofol combined in the same syringe has been

described in the emergency department (ED) as an induction regimen for rapid sequence intubation.

The most recent PSA combination to be described in the literature is that of low-dose ketamine and propofol ("ketofol").⁶

In this article we attempt to describe the postulated benefits of using these two agents together and examine the safety and efficacy of the combination and compared the efficacy with Ketamine and Midazolam combination.

2. Materials and Methods

The prospective randomised single blinded study was conducted at our hospital after approval from the Institutional Ethics committee on 22/09/2007 (letter no.AMS/DDHRC/142/07). All Adults aged between 15 to 60 years of both males and females under ASA Grade I and Grade II category who require procedural sedation and analgesia for minor surgeries and also who doesn't have any contraindication for conscious sedation were included in the study. Patients were excluded if they have uncontrolled HTN, drug allergies to the drugs in study, diabetes Mellitus, I schemic heart disease, asthma, tuberculosis, epilepsy, hypovolemia, hepatic, renal disease and neurological diseases, patients who were higher than ASA Grade 2 and the patients who require more than 30 min of sedation. Written informed consent was taken from all the participants prior to the start of the study.

The patients were randomly chosen according to the Age, Sex and Weight and divided into Two Groups of 25 patients each. In Group 1, patients were given the Ketamine and Propofol (Ketofol) combination 1:1.8 dilutions before the starting of the procedure and the dose was according to the patient's age and weight, 0.125 mg/kg Ketofol mixture (ketofol), 2 min subsequent to injection of 0.25 mg/kg each and maintained with 0.125 mg/kg as and when necessary. Ketofol was prepared by combining ketamine 1 mL (50 mg/mL), propofol 10 mL (10 mg/mL) in a 10ml single syringe. 1 mL of ketofol includes ketamine 5 mg and propofol 9 mg. In Group 2, patients received 1mg of Midazolam 3 to 5 min before followed by Ketamine 0.5 to 1.0 mg/kg, and then 10 to 20mg according to the need of the procedure.

All patients were placed on n on-invasive blood pressure, pulse oximeter, and nasal sample end tidal CO₂ (ETCO₂)⁷⁻⁹ monitors, as per standard guidelines for procedural sedation and analgesia Data were collected by trained anaesthesia assistant, no patient received supplemental oxygen. Baseline values were recorded. During the procedure, agents used and doses were recorded every 3 minutes on a chart. Furthermore, pulse oximetry, heart rate, blood pressure, respiratory rate, and ETCO₂ were monitored continuously and recorded every minute.

Data was collected during the procedure and were then entered into an Excel (Microsoft Corp., Redmond, WA)

database for further analysis. All analysis and interpretation of data was performed using SPSS Version 15.0 statistical analysis software. Data were analyzed using descriptive statistics.

The comparison between the two groups, Group 1 – Ketamine- Propofol combination (Ketofol) and Group 2 Ketamine and Midazolam combination was done using Two-Sample T-Test, a p value of < 0.05 is considered significant. With the help of SPSS version 15.0 Statistical calculator, we calculated Mean, Standard Deviation, SE mean, 95% CI, T-value, and p-value (Table 1) for all the parameters which were recorded.

Differential analysis was evaluated between groups for non-quantitative data using chi-square. For data which was regularly distributed, the independent-sample t -test and for irregularly distributed data the Mann Whitney U test was used to compare groups. Also we used the Wilcoxon test for irregularly distributed data, to evaluate the differences in the groups. Using 2 sample T-test, with alpha =/ < 0.05, Assumed standard deviation and target power was set and calculated the Sample size by using - Testing mean1 = mean2 (versus not =) Calculating power for mean 1 = mean2+ difference, Alpha = 0.05. Assumed standard deviation and difference was calculated for each parameter in the two groups, with the help of difference, and setting Target Power to 0.99, Sample size and Actual power was calculated for each group. Sample size calculated in previous studies showed a sample size of 5 to 17, and Actual power calculated with this sample size was 0.990 to 0.997 which shows significance of the study.

Power analysis was calculated with the same parameters which were set to measure sample size. Sample size was set at 25 which is fixed and the power calculated was 1.0.

3. Results

Our study included 50 patients of ASA Grade 1 and 2 with demographic characteristics (Table 2) like mean age of 40.64 in Group 1 (standard deviation [SD] 12.73, Mean age of 40.20 (SD–10.80) in Group 2, of these 32% belongs to 15 to 25 years, 28% belongs to 25 to 35 years, 20% belong to 35 to 45 years and remaining 20 % belongs to 45 to 60 years; 42% were Males – 20% in Group 1 and 24% in Group 2, 56% were Females – 30% in Group 1 and 26% in Group 2. With a Mean dose administered for Group 1 is (CI = 1.6 to 1.7) and for Group 2 is (CI = 2.4 to 2.5). and the Recovery time for Group 1 is (CI = 6.3 to 6.6) and for Group 2 is (CI = 8.8 to 9.4).

Intra Operative Mean PR (Heart Rate) (Graph 1) for Group 1 and 2 at 3 min (94.8, 116.24) with 95% CI = (-27.39, -15.81), 6 min (95.12, 120.20) with 95% CI= (-31.51, -18.73), at 9 min – (95.20, 120.50) with 95% CI= (-30.98, -19.58), at 12 min – (96.48, 117.50) with 95% CI= (-27.23, -14.82), at 15 min – (93.90, 119.10) with 95% CI= (-32.30, -18.02) at 18 min – (90.80, 118.60) with 95% CI = (-41.70,

-13.85).

Mean SBP for Group 1 and Group 2 at 3 min – (114.00, 147.20) with 95% CI – (-40.15, -26.25), 6min – (113.28, 146.32) with 95% CI – (-39.72, -26.36), 9min – (114.88,144.64) with 95% CI – (-35.87, -24.13), 12min – (112.86,142.00) with 95% CI – (-35.41, -22.87), 15min – (114.21, 141.05) with 95% CI – (-33.28, -20.40), 18 min –(108.00,139.00) with 95% CI – (-44.79, -17.21).

Mean DBP for Group 1 and Group 2 at 3 min (73.2, 89.20) with 95% CI – (-19.81, -12.19), 6min (71.20, 89.20) with 95% CI – (-21.92, -14.08), 9min (72.00, 88.00) with 95% CI – (-19.87, -12.13), 12min (72.38, 87.08) with 95% CI – (-19.35, -10.06), 15min (72.63, 86.67) with 95% CI – (-19.02, -9.06), 18min (70.00, 88.46) with 95% CI – (-27.71, -9.22).

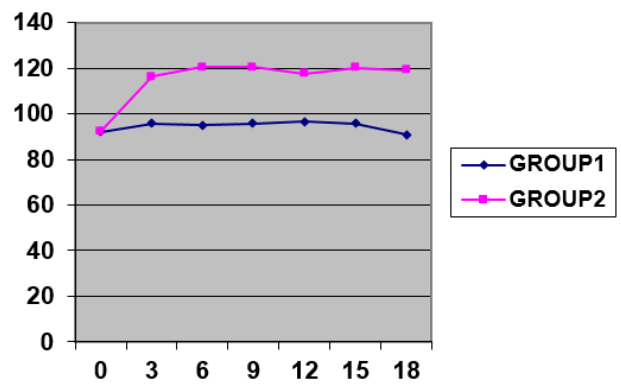


Fig. 1: Heart Rate trend

X-Axis - Pulse Rate, Y-Axis - Time (mins).

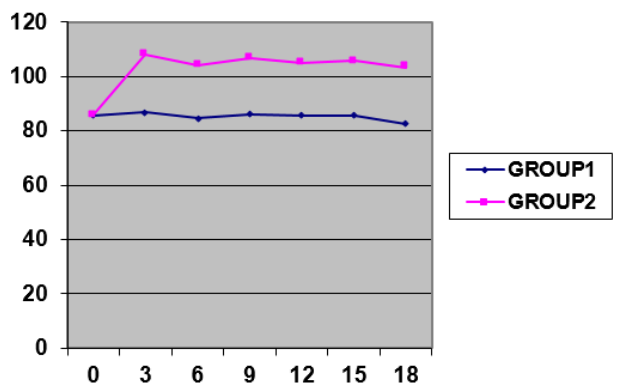


Fig. 2: Intra op Mean arterial pressure

X-Axis - Time (mins), Y-Axis - Mean Arterial blood pressure

Mean of MAP (Graph 2) for Group 1 and Group 2 at 3 min (86.76, 108.28) with 95% CI= (-25.70, -17.34), 6min (85.00, 107.88) with 95% CI – (-27.04, -18.72), 9min

Table 1: Statistical chart

Parameter	SD	Variance	T-Value	P
PR	15.3(11.1-16.8)	238.8(122-290)	7.15(-6.8 - -8.9)	0.000
SBP	17.4(10.2– 20.6)	314(104-426)	8.8(5.3 – 10.2)	<0.001
DBP	10.3(9.7 – 11.3)	107(94 – 129)	6.05(0.85 – 9.3)	< 0.001
MAP	12(9.1-13.6)	150(83-186)	8.99(5.5 – 11.0)	0.000
RR	2.1(1.56-2.63)	4.8(2.43-6.92)	0.54(-1.0- -.27)	0.60
SpO2	1.0(0.83-1.8)	1.1(0.48-3.2)	0.61(0.11-1.62)	0.63
Mean Dose	2.01	4.06	0.07	0.945
Recovery time	7.6	57.8	-13.76	0.000

Table 2:

S.No	Parameter	Group 1	Group 2
1.	Age – Mean	40.64	40.20
	SD	12.73	10.80
2.	Sex M/F	10(20%)/15(30%)	12(24%)/ 13(26%)
3.	Weight, Mean	53.96	53.54
	SD	6.63	4.36
4.	ASA I/II	25	25

(86.20, 106.88) with 95% CI – (-24.65, -16.71), 12min (85.71, 105.63) with 95% CI – (-24.59, -15.23), 15min (86.00, 105.89) with 95% CI – (-25.04, -14.75), 18min (82.60, 103.93) with 95% CI – (-30.78, -11.88). Patients in Group I maintained their blood pressures levels in near normal range to their baselines levels. Where as patients in Group II had an overshoot of their blood pressures all SBP, DBP and MAP for the initial first 8 to 12 min followed by returning to lower level, which still remained higher than the preoperative basal reading

Mean Respiratory Rate (RR) at 3min (24.72, 24.88) with 95% CI – (-1.36, 1.04), 6min (25.44, 25.68) with 95% CI – (-1.72, 1.24), 9min (24.72, 25.44) with 95% CI – (-2.10, 0.66), 12min (24.57, 24.83) with 95% CI – (-1.51, 0.98), 15min (23.79, 24.21) with 95% CI – (-1.65, 0.81), 18min (23.60, 24.00) with 95% CI – (-2.49, 1.69), Mean SPO2 at 3min (95.72, 95.72) with 95% CI – (1.04, 1.04), 6min (95.68, 95.24) with 95% CI – (0.10, 0.98), 9min (95.80, 95.44) with 95% CI – (0.14, 0.86), 12min (95.76, 95.79) with 95% CI – 0.58, 0.52, 15min (95.94, 95.89) with 95% CI-(0.59, 0.70), 18min (96.00, 96.15) with 95% CI-(1.40, 1.09), In our study Respiratory rate and saturation of oxygen were also measured at 3 min interval, both groups had rise in respiratory rate with acceptable level of fall In saturation. No patient had a fall of Spo2 of less than 94%. Both groups had similar changes in respiratory pattern and saturation levels which showed nil significance. Mean Recovery time (RT) for Group 1 and 2 are – (1.26 and 4.72) with 95% CI-(15.4, 11.4), Mean Dose used for Group 1 and Group 2 were 2.09 and 1.98 with 95% CI (1.11 and 1.19).

No complications were seen intra operatively in both the groups but in Group II adjuvant drug propofol added for 2 cases of reduction of dislocation of shoulder joints as ketamine in Group II caused muscular rigidity which

made the dislocation impossible to reduce without the adjunct propofol. Postoperatively in Group II 7 patients had experienced nausea, vomiting and 12 patients had delirium. In Group I only 2 patients had nausea and vomiting and 3 patients had delirium.

It was observed that the rise in pulse rate in Group I has regressed to preoperative level and the blood pressure maintained through out the intra operative and postoperative period. In Group II the rise in pulse rate and blood pressure remained above baseline level even in post operative period. Recovery time for Group I was earlier than that of Group II.

4. Discussion

One of the most important goals of Emergency physician¹⁰ is to provide patient comfort. Physicians often encounter patients who present with painful conditions such as lacerations, fractures, and dislocations that require the use of painful interventions. Furthermore, certain no painful procedures, such as computed tomography in a small child, may require the use of anxiolytic agents or behavioural control. When patients present to the emergency department, treating the pain and anxiety with both psychologically and pharmacologically that accompany the chief complaint are critical to patient satisfaction and quality of care and at the same time safety of the patient preventing adverse effects¹¹ especially in paediatric patients^{12,13} and efficacy of the drugs which they use are of utmost importance.

On the basis of recognition that proper administration of sedative medications is a continuum and it is often difficult to predict how an individual will respond to a specific sedative agent, practitioners should possess the skills required to rescue a patient one level greater than the

intended level of sedation. Therefore, should deep sedation be required to perform a procedure, the practitioner is expected to be competent in skills involving cardiovascular support and airway management as in general an anaesthesia. Due to emphasis in the emergency medicine training curriculum, these qualities are now considered core skills for all certified emergency physicians

The use of propofol and ketamine as single agents for procedural sedation and analgesia in the ED has grown in popularity⁶ but the unwanted effects of each drug alone have limited their adoption in select populations. This study represents a novel application of the combination of 2 well-known medications whose characteristics appear to be complimentary. Our study shows ketofol to be an effective and apparently safe drug for procedural sedation and analgesia regime than Ketamine and Midazolam combination.

The mixture of ketamine and propofol into a single syringe in a 1-to-2 ratio offers a simple, practical approach to medication preparation and use. This series used ketofol on patients of all ages between 15 to 60 of ASA Grade 1 and Grade 2 with a high degree of satisfaction, thus highlighting its versatility.

Results in our study showed that the mixture of ketamine and propofol in the same syringe is physically and chemically stable and showed more hemodynamic stability, recovery time is less, least side effects than individual drugs alone and with ketamine and midazolam combination which satisfies the criteria as an ideal agent for Procedural sedation.

5. Conclusion

Ketofol is better in maintaining hemodynamics throughout the procedure, recovery from anesthesia was more rapid after the last dose and few side effects like nausea, vomiting and emergence delirium, shorter stay than that of Ketamine and Midazolam combination.

6. Financial support and sponsorship

Nil.

7. Conflicts of interest

There are no conflicts of interest.

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Cite this article: Donda RK, Annareddy GR, Nattala R, Rani MU. **Clinical investigation on the analogy between the ketofol (Amalgamation of Ketamine and Propofol) and ketamine and midazolam for procedural sedation – A single blinded study.** *Indian J Clin Anaesth* 2020;7(1):112–116.