A Comparative Study on Three Different Combinations of Ketofol for Induction of General Anaesthesia

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ABSTRACT

BACKGROUND

Ketamine and propofol are one of the commonly used drugs for induction of general anaesthesia. Ketofol, is the combination of ketamine and propofol in varying concentrations. Due to the paucity of information in the literature regarding comparison of different combinations of ketofol for use as an induction agent, we intend to study the various doses of propofol ketamine combination in view of its haemodynamic stability and its relevance to speed of induction as well as side effect profile.

METHODS

This is a double blinded randomised controlled trial study. 60 patients posted for elective surgery under general anaesthesia were selected. They were randomly allotted to three groups with 20 patients in each group. Group 1 received ketofol in the ratio of 1:1, group 2 in the ratio of 1:2, group 3 in the ratio of 1:3. The time from the start of injection till the loss of verbal command, induction time, was noted. Mean arterial pressure, incidence of apnoea, awareness, hallucinations and post-operative nausea and vomiting (PONV) were noted.

RESULTS

Induction time was fastest in group 3 followed by group 2 followed by group 1. It was statistically significant. Mean arterial pressure (MAP) was comparable in all the three groups at different time intervals except at 5 minutes after induction, the fall in group 3 was significant. The change in MAP as compared to baseline in group 1 and 2 in different time intervals was not significant. But the fall in MAP was significant as compared to baseline in all the different time intervals in group 3. There was no reported incidence of apnoea, awareness and hallucinations in all the three groups. There were two reported cases of PONV in group 1, one in group 2 and zero in group 3.

CONCLUSIONS

Ketofol with the maximum propofol and least ketamine combination has the fastest induction time. Ketofol in the combination of 1:1 and 1:2 offers more haemodynamic stability as compared to 1:3 combination and ketofol has minimal side effects.

KEY WORDS

Ketofol, Different Combinations, Induction Time, Haemodynamic Stability

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DOI: 10.14260/jemds/2021/95

How to Cite This Article:
Chingtham B, Singh LC, Ramakrishna S, et al. A comparative study on three different combinations of ketofol for induction of general anaesthesia. J Evolution Med Dent Sci 2021;10(07):430-434, DOI: 10.14260/jemds/2021/95

Submission 29-10-2020,
Peer Review 17-12-2020,
Acceptance 23-12-2020,
Published 15-02-2021.

BACKGROUND

Ketamine and propofol are one of the common, generally accepted drugs to be used as an induction agent for general anaesthesia. Ketamine is a drug which stimulates the cardio – respiratory system. It directly causes an increase in cardiac output, arterial blood pressure, heart rate and central venous pressure.[1] However, very widespread use of this drug is limited due to its incidence of clinically significant psychomimetic effects.[2] On the other hand, propofol generally causes vasodilation, related to myocardial depression. But when propofol and ketamine are mixed together, both myocardial depression and vasodilation are found to be diminished due to the sympathetic stimulation offered by ketamine.[3] so this study was conducted to know the effect of their combination using, ketofol which is a mixture of propofol and ketamine in different concentrations.[1]

There have been documented studies for the use of these combinations of propofol and ketamine in many settings like an induction agent,[3,4,5,6] tubal sterilisation by minilaparotomy.,[7] medical termination of pregnancy.,[8] closed reduction of nasal fracture.,[9] gastrointestinal procedures.,[10,11,12] laryngeal tube suction.,[13] endotracheal intubations.,[14] and procedural sedations.[15]

Many studies have been conducted comparing the combination of these two drugs that is ketamine and propofol over the individual drugs. Comparisons were done generally in areas of haemodynamic stability, sedation score, mean recovery times, side effects etc. Such studies revealed the advantages of using ketofol over the individual drugs.

It was found to be a safe and useful technique for procedural operations in ambulatory settings. It was also found that with the use of the combination of these two drugs, that is ketofol, patient's mood was significantly better and also it was found that cognitive function recovered more rapidly in those who received ketofol as compared with those patients who received higher doses of ketamine.[2]

In another study, ketofol was found to be associated with improved hemodynamic stability and demonstrated the potentiality of using as an alternative agent for emergency induction where stable hemodynamics are needed.[3]

Ketofol was found to be a safe and effective alternative induction agent that does not have many side effects of its two different components.[4]

Different combinations of ketofol mixture provided appropriate haemodynamic conditions and sufficient sedations. Ketamine combinations were found to be associated with a shorter mean recovery time as compared to propofol. But the haemodynamic stability and satisfaction scores were similar, and without any important side effects in gastrointestinal interventions.[11]

Propofol and ketamine combination, that is, ketofol was found to be associated with greater satisfaction scores and a shorter recovery time than propofol, which also does not have adverse effects in endoscopic retrograde cholangiopancreatography.[12]

But ample scientific literature on comparisons of different combinations of ketofol for use as an induction agent was lacking. Hence, this study was conducted.

Here, we wanted to study three different combinations of ketofol, ketamine : propofol combination (1:1), (1:2) and (1:3) as an induction agent in terms of induction time, haemodynamic parameters at varied interval of time and adverse reactions, if any.

METHODS

Our study was a randomised controlled trial conducted in the Department of Anaesthesiology, RIMS, Imphal, and Manipur from September 2019 to August 2020. All patients aged 18 to 60 years, American society of Anaesthesiologists (ASA) grade I and II undergoing elective surgery under general anaesthesia were enrolled. The exclusion criteria were patients with diabetes, hypertension, pregnancy, history of breast feeding, respiratory, cardiac, neurological, renal, liver disease, any known allergy to drugs used for induction of anaesthesia and psychiatric patients.

After obtaining the approval from the ethical committee, 60 patients fulfilling the inclusion criteria were enrolled. (Sample size was calculated based on the study conducted by Aboeldahab H, Samir R, Hosny H, Omar A[4] and using the formula $n = (u + v)^2 (s_1^2 + s_2^2) / (m_1 - m_2)^2$, where u = power of 80 %, v = 95 % confidence interval, s_1 = SD at baseline, s_2 = SD after intervention. Using this formula n = 16, and considering a non-response rate of 20 %, n = 20. So, for three groups n = 20 x 3, which is equal to 60.) Using a computer generated randomisation chart, they were randomly allotted by a person not directly involved in the study into three groups namely group 1, group 2 and group 3 consisting of twenty patients each. Both the patient and the primary investigator were blinded. A pre-operative visit was done a day before surgery so that a good rapport was established. All the patients included in this study received tablet alprazolam 0.25 mg the night before surgery and fasted for 6 hours prior to anaesthesia. In the pre-operative holding area, intravenous access was secured, and patients were pre medicated with injection glycopyrrolate at the dose of 0.004 mg / kg.

On arrival to the operation theatre, baseline monitoring of pulse rate [PR], non-invasive blood pressure [NIBP], oxygen saturation [SPO2] and electrocardiogram [ECG] were started. After pre oxygenation for 3 minutes with face mask, all patients received intravenous butorphanol [10 mcg / kg] and patients randomly allotted in group 1 received ketofol combination of 1:1. Ketamine was prepared as 1 mg / kg body weight and propofol 1 mg / kg body weight. Patients allotted in group 2 received ketofol combination of 1:2. Ketamine was prepared as 0.66 mg / kg body weight and propofol as 1.33 mg / kg body weight. Patients in group 3 received ketofol combination of 1:3. Here, ketamine was prepared as 0.5 mg / kg body weight and propofol prepared as 1.5 mg / kg body. Preparation of the drug was done by an anaesthesiologist not directly involved in the study. All the drug combinations were prepared as a total of 2 mg / kg body weight. The study drug was given over a period of 30 seconds. Induction time was noted, which is defined as the time taken from the start of the injection till the loss of verbal command. Patients who couldn't be induced with the calculated study dose were excluded from the study. Both the patient and the primary investigator were blinded to the induction agent given.

Haemodynamic variables were measured before induction (baseline), just after induction and also at 1, 2, 3, 4 and 5 minutes after induction. After the data collection, patient was intubated using suitable muscle relaxant. The surgical

procedure was then started and the remainder of anaesthetic management was left upon the direction of the consultant anaesthesiologist. It is to be noted that the patient did not undergo any intervention and no external stimulus was applied during the time-period when the data was collected. After the procedure, recall of events, awareness, hallucinations and euphoria in post anaesthetic care unit (PACU) were noted. Incidence of apnoea / post-operative nausea and vomiting were also checked. Data collected was checked for completeness and consistency.

Statistical Analysis

Data was entered in International Business Machines Statistical Package for the Social Sciences (IBM SPSS) statistics version 21 for windows [IBM Corp.1995, 2012]. Descriptive summary was summarized in mean, standard deviation, frequency and percentage. To compare between groups, mean difference with analysis of variance (ANOVA) was used. To compare within the group, paired t test was used.

RESULTS

Parameters	Group 1	Group 2	Group 3	P-Value
Age (years)	34.70 ± 12.53	35.25 ± 11.43	39.63 ± 15.35	0.21
ASA (I:II)	20:0	19:1	16:4	0.06
Sex (M:F)	6:14	4:16	5:15	0.77

Table 1. Demographic Profile

From this table, it is shown that the demographic profile between the three groups were comparable in all the three aspects. The variation among them was not significant as indicted by the P value. That is, mean age distribution between the three groups, distribution of ASA I and II, male and female in the three groups were comparable.

Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	P-Value
46.90 ± 4.06	39.35 ± 3.79	33.15 ± 2.98	0.00

Table 2. Mean Induction Time of the Three Groups (in Seconds)

Map	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	Group 3 (Mean ± SD)	P-Value
Baseline	92.25 ± 12.32	90.60 ± 12.00	92.60 ± 8.74	0.83
After induction	88.20 ± 16.98	89.60 ± 11.09	85.55 ± 9.97	0.61
1 min	90.90 ± 15.73	89.55 ± 11.86	83.35 ± 7.56	0.12
2 min	88.15 ± 13.55	91.20 ± 15.22	80.85 ± 14.24	0.07
3 min	89.40 ± 14.21	89.50 ± 16.20	81.85 ± 15.39	0.20
4 min	88.75 ± 12.52	87.60 ± 15.95	79.50 ± 14.08	0.09
5 min	90.90 ± 13.16	90.65 ± 15.66	80.50 ± 15.43	0.04

Table 3. Mean MAP of the Three Groups

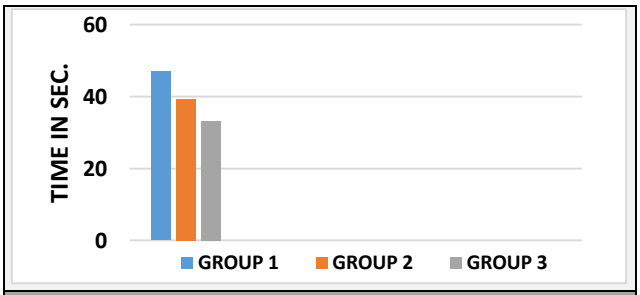

Figure 1. Mean Induction Time of the Three Groups in Seconds

As seen from table no 2, the induction time decreases as we go from group 1 towards group 3. The difference was statistically significant as indicated by the P-value. It was graphically represented in figure 1 where we saw the decline in induction time as we go from group 1 towards group 3

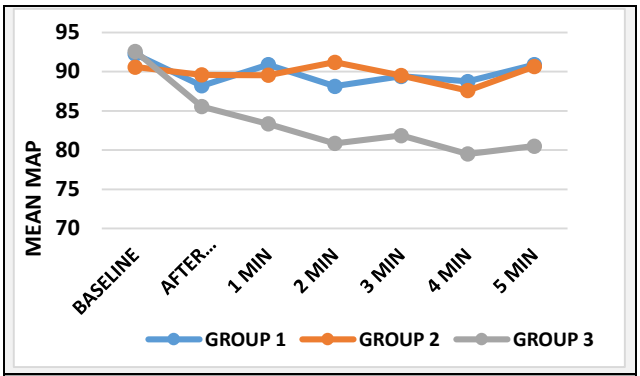

Figure 2. Mean MAP of the Three Groups at Different Time Intervals

From this table and graph we see that the MAP was comparable at the baseline as compared between the three groups and the change in MAP was also not significant as compared between the three groups at all-time intervals except at 5 minutes after induction.

Parameters	Group 1 Mean Difference ± SD	Group 1 P Value	Group 2 Mean Difference ± SD	Group 2 P Value	Group 3 Mean Difference ± SD	Group 3 P Value
Baseline - just after induction	4.05 ± 9.00	0.06	1.00 ±5.45	0.43	7.05 ± 9.52	0.004
Baseline - 1 min	1.35 ± 11.34	0.60	1.05 ± 8.11	0.57	9.25 ± 9.32	0.000
Baseline - 2 min	4.10 ± 9.28	0.06	- 0.60 ± 11.90	0.82	11.75 ± 13.23	0.001
Baseline - 3 min	2.85 ± 8.54	0.15	1.10 ± 9.51	0.61	10.75 ± 13.37	0.002
Baseline - 4 min	3.50 ± 8.13	0.07	3.00 ± 7.80	0.11	13.10 ± 13.62	0.000
Baseline - 5 min	1.35 ± 8.61	0.49	- 0.05 ± 10.83	0.98	12.10 ± 15.32	0.002

Table 4. Comparison of the Change of MAP from Baseline in the Three Groups

From this table, we see that the change in MAP from baseline was not significant at different time intervals in group 1 and 2. But it was significant statistically in all the recordings in group 3, and from table 3, we can see that there was a fall of mean MAP from baseline at all the recordings in group 3. So, we can infer that group 1 and 2 have a stable MAP but in group 3, there was a significant fall in MAP after induction with the drug. There was no reported case of recall of events, awareness, hallucination and euphoria in all the three groups. P-value as calculated by chi-square was 0.349 which was not significant.

PONV	Group 1	Group 2	Group 3
Yes	2	1	0
No	18	19	20

Table 5. Post-Operative Nausea and Vomiting

DISCUSSION

We all know that propofol and ketamine are commonly used drugs as an induction agent in general anaesthesia, and also, we have encountered the combined use of these drugs many times with great success for the past so many years. But we feel that not sufficient studies were there in scientific literature about the different combinations of these drugs for

use as an induction agent for general anaesthesia. Hence, we decided to take up this study.

In this study, we found that when we use different combinations of Ketofol, the fastest induction was found in group with the maximum propofol dose and minimum ketamine dose and the slowest with the least propofol and maximum ketamine. The induction time was measured from the start of the injection of the drug till the loss of verbal command. This was done by explaining to the patients beforehand. We let the patient count numbers nonstop as soon as we tell them to do so. The moment the patient stops counting, it is taken as induction time.

The difference in the induction time can be attributed to the difference in onset of action of the individual drugs. That is, the usual onset of action of ketamine is 30 - 60 seconds.[16,17] While that of propofol is 30 - 40 seconds.[18] In line with our result, Hesham Aboeldahab[4] and his colleagues found that time for loss of verbal contact was found to be maximum in ketamine group followed by ketofol followed by propofol group.

In this current study, we found that group 1 and group 2 (ketofol in the ratio of ketamine: propofol of 1:1 and 1:2) showed more stable haemodynamics in comparison to 1:3 group. When compared between the three groups, there was significant fall in MAP in group 3 at 5 minutes after induction, and when compared within the group, there was no significant change in MAP in group 1 and group 2 but the fall in MAP in group 3 was significant as compared to baseline at all the different time interval of recordings.

In a similar finding to our study, Kurdi MS and Deva RS [7] in their study found that there was no statistically significant difference in haemodynamic parameters between the ketofol in 1:1 and 1:2 ratio. In both the groups, haemodynamic stability was maintained. Also, a study conducted by Aydogomus MT and his colleagues.[10] demonstrated a stable haemodynamic parameters for ketofol in the ratio of 1:2, and in a study conducted by Aboeldahab H and his colleagues.[4] (2011) found a stable hemodynamic reading for ketofol group of 1:1.

But contrary to our finding, for the group of 1:3 combination Baker MA and his colleagues (2018) and also Ayotallahi V and his colleagues (2016) observed a haemodynamic stability in their studies. The difference in the findings can be explained by the difference in the drug doses.

In the study conducted by Baker MA and his colleagues[12] the drug was prepared in a 20 ml syringe with 1 % 15 ml propofol + 1 ml 50 mg / ml ketamine + 4 ml saline such that each ml contained 0.75 mg propofol and 0.25 mg ketamine. The drug was administered until Ramsay sedation scale increased to 3 - 4. Supplementary study drug was added (intravenous 0.5 - 1 mg / ml) in case of need. Also, in a study conducted by Ayotallahi V[9] (2016) for 1:3 combination, the drug was prepared by adding 150 mg propofol plus 50 mg ketamine with distilled water to make 16 cc volume. The drug was slowly injected till Ramsay sedation scale 6 was reached.

But in our study, we used a fixed dose. It was calculated based on per kg body weight that is 0.5 mg / kg of ketamine and 1.5 mg / kg of propofol. The difference in the finding may be due to usage of more propofol or less ketamine in our study than theirs.

In our study, we found that two patients complained of PONV in group 1 and one patient in group 2 and zero in group 3. Statistically, they are insignificant. Similar findings were also observed in studies conducted by Aboeldahab and his colleagues (2011) and Dabbiss M and his colleagues (2009).

CONCLUSIONS

If faster induction is required, we can choose a combination with more propofol and less ketamine. Ketofol in the combination of 1:1 and 1:2 offer a better haemodynamic stability with fewer side effects.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jemds.com.

REFERENCES

[1] Amornyotin S. Ketofol: a combination of ketamine and propofol. J Anesth Crit Care Open Acess 2014;1(5):00031.
[2] Daabiss M, Elsherbiny M, Al-otibi R. Assessment of different concentration of ketofol in procedural operation. BJMP 2009;2(1):27-31.
[3] Smischney NJ, Beach ML, Loftus RW, et al. Ketamine/propofol admixture (ketofol) is associated with improved hemodynamics as an induction agent: a randomised, controlled trial. J Trauma Acute Care Surg 2012;73(1):94-101.
[4] Aboeldahab H, Samir R, Hosny H, et al. Comparative study between propof, ketamine and their combination (ketofol) as an induction agent. Egypt J Anaesth 2011;27(3):145-50.
[5] Hui TW, Short TG, Hong W, et al. Additive interactions between propofol and ketamine when used for anaesthesia induction in female patients. Anaesthesiology 1995;82(3):641-8.
[6] Elzayyat NS, Hassan AR, ElSakka AI, et al. Ketamine/propofol (ketofol) versus propofol/fentanyl for induction of anaesthesia in parturients with rheumatic valvular lesions undergoing elective cesarean section. Egypt J Cardiothorac Anesth 2013;7(2):79-84.
[7] Kurdi MS, Deva RS. A comparison of two different proportions of ketofol with fentanyl-propofol for sedoanalgesia for tubal sterilization by minilaparotomy: a randomised double -blind trial. J Obstet Anaesth Crit Care 2015;5(2):84-9.
[8] Wang Y, Jiang X, Pang L, et al. A randomised double- blind controlled study of the efficacy of ketofol with propofol-fentanyl and propofol alone in the termination of pregnancy. Afr J Phar Pharmacol 2012;6(34):2510-4.
[9] Ayatollahi V, Vafaiyan M, Hatami M, et al. Two different concentrations of ketofol for procedural sedation and analgesia in closed reduction of nasal fracture. J Craniofac Surg 2016;27(4):996-1000.
[10] Aydogmus MT, Turk HS, Oba S, et al. A comparison of different proportions of a ketamine-propofol mixture administered in a single injection for patients undergoing colonoscopy. Arch Med Sci 2015;11(3):570-6.
[11] Aydogan H, Aydogan T, Koglu AU, et al. Propofol-ketamine combination has shorter recovery times with similar

hemodynamics compared to propofol alone in upper gastrointestinal endoscopy in adults. A randomised trial. Acta Medica Mediterr 2013;29:259-64.

[12] Baker MA, Ibrahim NM, Mackey MM. Hemodynamic stability of ketamine/propofol admixture ketofol in patients undergoing endoscopic retrograde cholangiopancreatography. J Curr Med Res Pract 2018;3(1):43-6.

[13] Ozgul U, Begec Z, Karahan K, et al. Comparison of propofol and ketamine-propofol mixture (ketofol) on laryngeal tube-suction II conditions and hemodynamics: a randomised, prospective, double-blind trial. Curr Ther Res Clin Exp 2013;75:39-43.

[14] De Moraes AG, Africano CJR, Hoskote SS, et al. Ketamine and propofol combination (ketofol) for endotracheal intubations in critically ill patients: a case series. Am J Case Rep 2015;16:81-6.

[15] Miner JR, Moore JC, Austad EJ, et al. Randomized, double-blinded, clinical trial of propofol, 1:1 propofol /ketamine and 4:1 propofol/ketamine for deep procedural sedation in the emergency department. Ann Emerg Med 2015;65(5):479-88.

[16] Abola R, Geralemou S, Szafran M, et al. Intravenous anesthetics. In: Barash PG, Cullen BF, Stoelting RK, et al. eds. Clinical Anesthesia. 8th edn. Philadelphia: Wolters Klumer 2017: p. 1270.

[17] Vujk J, Sitsen E, Reekers M. Intravenous anesthetics. Miller RD, Cohen NH, Eriksson LI, et al. eds. Miller's Anesthesia. 8th edn. Canada: Elsevier Saunders 2015: p. 847.

[18] Scarth E, Smith S. Drugs in anaesthesia and intensive care. 5th edn. USA: Oxford University Press 2016: p. 326.