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Research Article

Comparative study between propof, ketamine and their combination (ketofol) as an induction agent

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KEYWORDS

Ketamine;
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Abstract *Introduction:* Ketofol is a new combination formed by mixing ketamine and propofol. This mixture was used for procedential sedation. However, little is known about its hypnotic characteristic as an induction agent.

Methods: Sixty patients were allocated into three equal groups (20 patients each) subjected to hernia repair surgeries under general anesthesia. These patients were anesthetized using propofol (group P), ketamine (group K) and ketofol (group KP) as induction agents. The time needed for loss of verbal contact, eyelash reflex and their corresponding BIS values were recorded. Mean arterial blood pressure and heart rate were measured. Incidence of apnea, postoperative nausea and vomiting, awareness and hallucination were noted.

Results: The time needed for loss of verbal contact and eyelash reflex was earlier in group P followed by group KP and group K, respectively, the difference was statistically significant. After induction, MAP decreased in group P, increased in group K while it remained comparable to baseline in group KP. The difference between groups was statistically significant. After intubation MAP increased in the three groups, it was comparable between KP and P groups but remained significantly higher in K group. After induction, HR decreased in P group, increased in K group while it remained comparable to baseline in KP group. The difference between groups was statistically significant. After intubation HR increased in the three groups, it was significantly higher in group K in comparison to groups P and KP, and as regards KP group HR was significantly higher than P group. Afterwards, HR decreased in the three groups and remained stable and comparable for the

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rest of the surgical time. The Bispectral index readings of ketofol group showed intermediate values between the other two groups.
Conclusion: Ketofol is a safe, effective alternative induction agent that lacks many side effects of its two components.

1. Introduction

Ketamine is an intravenous anesthetic developed in 1960s from its precursor phencyclidine and its mode of action is through causing dissociative anesthesia [1]. Several advantages have been attributed to ketamine starting from its amnesic and analgesic effects, maintenance of muscle tone, protecting airway reflexes and spontaneous respiration. However, ketamine has many side effects that limited its frequent use as an anesthetic. These side effects include nausea, vomiting, emergence hallucinations, elevation of blood pressure and heart rate due to its sympathomimetic effects and also it was presumed to increase intracranial pressure [2,3].

Propofol is a 2,6-diisopropylphenol [4] which was developed in Europe in the 1970s, it was utilized progressively in USA in the subsequent two decades [4,5]. It produces general anesthesia by facilitation of inhibitory neurotransmission mediated by GABA. Its main advantages are its rapid induction and recovery, antiemetic effects and anticonvulsant effects. Its main disadvantages lie in its dose dependent hypotension and respiratory depression [6,7].

It was postulated that combining both drugs will result in a mixture which has additive effects so that we can decrease the dose used from each drug and benefit from advantages regarding amnesia, analgesia, hypnosis and hemodynamic stability and on the other hand lessen the disadvantages attributed to either drugs [8]. This mixture was named ketofol and was assessed as a sedative agent in several studies mainly as in emergency departments with encouraging results [8]. In the present study, we aimed to assess the value of ketofol, when used as an induction agent, regarding its hypnotic criteria, both clinically and by BIS index readings, hemodynamic parameters, and the incidence of adverse effects of ketofol compared to its two constituents ketamine and propofol.

2. Patients and methods

After approval of the ethical research committee in Kasr El Aini hospital Cairo University and obtaining informed written consent, 60 adult participants aging 20–50 years old, ASA physical status I and II, without history of cardiovascular or neurologic disease undergoing hernia repair operations were enrolled in a randomized prospective comparative study. No premedication was given to the patients and no medications were allowed within 12 h prior to surgery. Upon arrival at the operating room, preoxygenation was started for 5 min during which the standard monitors; electrocardiogram, non-invasive blood pressure and pulse oximetry were attached to the patient. BIS monitor electrodes (Aspect Medical System, Vista^{TM}, MA, USA) were placed on the skin of the forehead after cleansing with alcohol. Thereafter baseline vital parameters were recorded and five successive readings of BIS at 30 s intervals were taken to obtain baseline value while the patients were fully awake, then patients were randomized into three groups, 20 patients each, group K (ketamine), group P (propofol), group KP (ketofol). Methods of randomisation was by a closed envelope chosen by the surgeon.

Prior to induction, all patients in the three groups received 2 ml of lidocaine intravenously to lessen pain on injection especially in the P and KP groups.

Induction of general anesthesia started as follows:

- Group K received intravenous ketamine in a dose of 2 mg/kg over 20 s, syringe contained 200 mg ketamine HCL (50 mg/ml) mixed with16 ml normal saline to reach a total volume of 20 ml given that each ml contained 10 mg of ketamine and hence 1 ml ketamine syringe for every 5 kg.
- Group P received intravenous propofol 1% in a dose of 2 mg/kg over 20 s, given that each ml contained 10 mg propofol and hence 1 ml propofol syringe for every 5 kg.
- Group KP received intravenous ketofol, prepared in a ratio of 1:1 as follows, 100 mg ketamine (50 mg/ml) diluted with glucose 5% to reach a volume of 10 ml + 100 mg propofol 1%, total volume is 20 ml each ml containing 5 mg propofol + 5 mg ketamine, the dose given was 1 ml for every 5 kg supposed to be equipotent to the dose used of each drug solely in the other two groups.

After 2 min of the start of induction, all patients received 2 ucg/kg fentanyl and 0.5 mg/kg atracurium and were mechanically ventilated with isoflurane 1.5% end tidal in 100% O_2 using the following parameters: tidal volume 6–8 ml/kg, respiratory rate 10–12 min to achieve end tidal CO_2 of 30–35 MmHg, 3 min later the patients were intubated, and maintained on 1.5% end tidal isoflurane. Intermittent boluses of atracurium were given throughout the operation and at the end of the surgery any residual neuromuscular block was reversed using neostigmine 0.05 mg/kg and atropine 0.02 mg/kg. The patients were then transferred to the post anesthesia care unit (PACU) and discharged when Alderete score was 10 [9].

3. Data collected

- Time needed for loss of verbal contact.
- Time needed for loss of eyelash reflex.
- BIS values were recorded at the following interval: at baseline, 5 s after loss of verbal contact, 5 s after loss of eyelash reflex, 2 min after induction, just before intubation, 1 min after intubation then every 15 min till end of surgery.
- Hemodynamic parameters (mean blood pressure and heart rate) were recorded before induction (taken as a baseline value), 2 min after induction, after intubation, 5 min after intubation and every 15 min till the end of surgery.
- All the patients were asked about recall of events or awareness and assessed for hallucinations and euphoria in the PACU.
- Incidence of apnea and postoperative nausea and vomiting was recorded.

4. Statistical analysis

Data are statistically described in terms of mean ± SD, frequencies (number of cases) and percentages as appropriate. Continuous data were analyzed done using two-way ANOVA for repeated measurements with post hoc Tukey's honest significant difference test. Qualitative data were compared using Chi-squared (χ^2) test with Yates correction. *P*-values less than 0.05 were considered statistically significant. All data were analyzed using SPSS 15.0 for windows (SPSS Inc., Chicago, IL, USA).

5. Results

There were no significant differences in demographic data between the three groups as regards patients' age, sex, height, body weight and ASA physical status (Table 1).

Regarding the time needed for loss of verbal contact and loss of eyelash reflex, patients in group K showed higher readings which were statistically significant relative to the other two groups. Patients in group KP lost the reflexes later than patients in group P, and there were a statistically significant difference between the two groups (Table 2).

5.1. Regarding hermodynamic effects between groups

- At baseline mean arterial blood pressure was comparable between groups.
- After induction, MAP decreased in group P, increased in group K while it remained comparable to baseline in group KP. The difference between groups was analyzed and found to be statistically significant.
- After intubation MAP increased in the three groups, it was comparable between KP and P groups but remained significantly higher in K group. Afterwards, MAP was comparable among the three groups (Table 3).

Table 1 Demographic data (data are expressed as mean ± standard deviation or ratio).

	Group P	Group K	Group KP
Age (years)	30.3 ± 6.3	31.6 ± 6.9	33.45 ± 7.7
Sex; M/F	17/3	16/4	18/2
Height (cm)	166.9 ± 7.16	164.7 ± 7.1	163.3 ± 7.7
Body weight (kg)	81.8 ± 9.26	83.6 ± 8.6	79.2 ± 9.8
ASA grade I/II	10/10	11/9	12/8

5.2. Regarding heart rate between groups

- Base line heart rate (HR) was comparable between the three groups.
- After induction, HR decreased in P group, increased in K group while it remained comparable to baseline in KP group. The difference between groups was analyzed and found to be statistically significant.
- After intubation HR increased in the three groups, it was significantly higher in group K in comparison to groups P and KP, and as regards KP group HR was significantly higher than P group.
- Afterwards, HR decreased in the three groups especially in group K, and remained stable and comparable for the rest of the surgical time.

5.3. Regarding BIS value between groups

Regarding BIS value, all groups showed BIS values around 95 before induction.

With the start of IV induction, patients in the three groups showed progressive loss of consciousness proved by loss of verbal and eyelash reflexes. BIS values were significantly different among the three groups as follows:

- In group P, BIS started to decrease with the initiation of IV injection to reach readings around 65 five seconds after loss of verbal contact and around 50 five seconds after loss of eyelash reflex, values continued to decrease to reach

Table 3 Mean blood pressure (MAP) in MmHg (data are expressed as mean ± SD) during the follow-up period.

Group	P (n = 20)	K (n = 20)	KP (n = 20)
Baseline	81.50 ± 4.513	82.95 ± 4.98	80.10 ± 4.40
After induction	76.65 ± 4.42[c]	88.30 ± 4.04[a,c]	80.65 ± 4.00[b]
After intubation	83.25 ± 4.14	91.50 ± 3.54[a,c]	83.10 ± 4.09
5″	80.00 ± 3.86	80.25 ± 2.97	82.15 ± 4.20
20″	82.70 ± 3.65	81.25 ± 2.35	81.20 ± 3.75
35″	81.30 ± 2.77	81.60 ± 2.23	82.60 ± 3.11
50″	81.88 ± 2.47	82.40 ± 2.23	81.00 ± 3.17
65″	82.11 ± 2.14	84.20 ± 2.44	83.10 ± 5.03
80″	79.40 ± 1.63	80.85 ± 2.92	80.47 ± 3.65
Extubation	85.66 ± 3.43	85.75 ± 2.67	83.90 ± 3.30

P; K; KP.
[a] Statistically significant relative to the other two groups.
[b] Statistically significant relative to group P.
[c] Statistically significant relative to baseline.

Table 2 Time needed for loss of verbal contact and loss of eyelash reflex (data are expressed as mean ± SD).

	Group P	Group K	Group KP
Time for loss of verbal contact (s)	31.80 ± 1.64	46.05 ± 1.93[a]	37.40 ± 2.50[b]
Time for loss of eyelash reflex (s)	36.90 ± 2.07	54.20 ± 2.82[a]	45.60 ± 2.41[b]

[a] Statistically significant relative to the other two groups.
[b] Statistically significant relative to group P.

readings around 45 two minutes after start of induction and these readings were statistically significant relative to the other two groups.
- In group K, BIS remained stable in comparison to baseline readings, values were around 95 five seconds after loss of verbal contact, 94 five seconds after loss of eyelash reflex and 94 two minutes after induction.
- In group KP, BIS started to decrease with the start of IV injection to reach readings around 85 five seconds after loss of verbal contact and 75 five seconds after loss of eyelash reflex, values continued to decrease to reach readings around 70 two minutes after start of induction. And these readings were statistically significant relative to group K.

After administration of atracurium, fentanyl and ventilation with isoflurane 1.5% for 3 min, all readings drifted down in K and KP group to reach a value of 55 while in P group, it reached a value of 41 (see Tables 4–6).

After intubation, readings slightly increased in the three groups with no statistical significant differences.

Five minutes after start of mechanical ventillation all data were comparable and remained comparable till extubation.

Table 4 Heart rate (HR) (beat/minute)during during the follow-up period (data are expressed as mean ± SD).

Group	P	K	Ketofol
Baseline	71.95 ± 5.69	72.85 ± 4.47	74.45 ± 6.03
After induction	67.25 ± 3.98	83.70 ± 6.90[a,c]	78.05 ± 5.20[b]
After intubation	74.65 ± 4.56	91.70 ± 8.56[a,c]	80.30 ± 3.61[b,c]
5″	71.01 ± 4.24	83.80 ± 6.03[a,c]	76.80 ± 4.03[b]
20″	69.75 ± 3.07	72.35 ± 4.88	71.15 ± 3.08
35″	70.40 ± 4.21	69.85 ± 4.38	71.05 ± 3.08
50″	70.27 ± 6.11	70.95 ± 2.41	71.35 ± 2.45
65″	68.17 ± 3.71	71.15 ± 1.98	69.75 ± 2.26
80″	73.01 ± 1.85	71.95 ± 2.06	73.15 ± 1.97
Extubation	81.73 ± 3.93[c]	81.65 ± 2.85[c]	81.65 ± 2.60[c]

[a] Statistically significant relative to the other two groups.
[b] statistically significant relative to group P.
[c] statistically significant relative to baseline.

Table 5 Descriptive statistics and test of significance for the effect of group on BIS during the follow-up period (data are expressed as mean ± SD).

Group	P	K	Ketofol
Baseline	95.10 ± 0.71	95.30 ± 1.031	95.10 ± 0.71
5 s after loss of verbal	65.01 ± 1.45[a]	94.65 ± 0.988	85.40 ± 3.78[b]
5 s after loss of eyelash	50.01 ± 2.65[a]	94.35 ± 1.089	75.40 ± 2.50[b]
2 min after induction	45.45 ± 1.64[a]	94.56 ± 1.319	70.25 ± 3.02[†]
Before intubation	41.86 ± 2.64[a]	55.55 ± 1.905	55.00 ± 1.45
After intubation	47.45 ± 2.46[a]	58.35 ± 1.461	57.80 ± 1.67
5″	48.90 ± 3.17	49.95 ± 3.546	50.60 ± 3.06
20″	49.65 ± 3.10	50.40 ± 4.547	49.65 ± 3.10
35″	51.45 ± 3.50	51.45 ± 3.502	52.85 ± 2.34
50″	51.83 ± 3.82	52.05 ± 3.052	52.05 ± 3.05
65″	53.05 ± 3.99	53.05 ± 2.139	53.85 ± 2.64
80″	55.23 ± 2.68	54.50 ± 1.823	53.84 ± 2.52
Extubation	84.10 ± 4.64	83.85 ± 3.760	85.80 ± 3.23

[a] Statistically significant relative to the other two groups.
[b] Statistically significant relative to group k.

Table 6 Regarding postoperative hallucinations, recall or awareness, it did not occur in any patient in the three groups.

	Group P	Group K	Group KP
Apnea	2	0	0
Nausea or vomiting	0	2	0

Statistically significant relative to group K.

After stoppage of muscle relaxants and inhalational anesthetics, all the patients regained consciousness within comparable time among the three groups.

5.4. Regarding postoperative nausea and vomiting

- In group K, 2 patients experienced nausea they were treated with ondansterone 4 mg.
- In groups P and KP none of the patients experienced nausea or vomiting.
- Apnea occurred only in propofol group in 2 patients.

Regarding postoperative hallucination, recall or awareness, they did not ocurr in any patient in the three groups.

6. Discussion

The combined use of ketamine and propofol has been addressed with great success in anesthesiology for many years. To the best of our knowledge very little is known in scientific literature about the use of ketofol (as a drug in a single syringe) as an induction agent compared to propofol and ketamine [10,11].

The main finding of our study was that when ketofol mixture was used as an induction agent, it showed an intermediate onset of hypnosis relative to its two constituents, provided hemodynamic stability and lower incidence of complications. In addition, the BIS readings in ketofol group showed intermediate values relative to the other two groups when correlated to the clinical end points of hypnosis.

In the current study, the KP group showed intermediate onset of clinical hypnosis proved by the time needed for loss of verbal response and loss of eyelash reflex. In contrast to our finding; Frey and his colleagues [12] randomized 70 elderly patients to receive either propofol in small boluses or propofol in small boluses with the addition of ketamine (30 mg) in the first bolus. They demonstrated that the use of ketofol was associated with shorter time until sedation when compared to propofol. In the current study; we used an equipotent dose of ketamine and propofol which could explain the difference between our findings and their findings.

In the study described herein, the ketofol group showed a more stable hemodynamics in comparison to the other groups. In line with our results, Arora et al. [13] studied 10 adult patients (over age 18) for procedural sedation given ketofol in 1:1 ratio and proved the hemodynamic stability of this mixture. Also Akin et al. [14] who found hemodynamic stability of ketofol in children undergoing cardiac catheterization. This is consistent with the result of HUI. et al. [15] who found improved cardiovascular stability when using different mixtures of propofol and ketamine in comparison to either drugs used solely.

In the KP group, BIS started to decrease with the start of IV injection to reach values around 85 with the loss of verbal contact and 75 with loss of eyelash reflex, values continued to decrease to reach readings around 70 two minutes after start of induction which is the time needed for both drugs to reach their peak effect. BIS values in this group could be explained by the opposing effects of its both constituents upon EEG activity and hence the reading of BIS. In a study by Sakai et al. [16] in 1999 who considered the effect of variable doses of ketamine given as a bolus followed by small dose propofol and ketamine infusion on the endpoints of hypnosis and BIS index, they found additive interaction between propofol and ketamine for achieving the hypnotic endpoints; however, the mixture did not depress the BIS values in proportion to its hypnotic effect and this was attributed to the small concentration of propofol used and/or ineffectiveness of ketamine on BIS.

Just before intubation BIS value decreased in the three groups due to administration of isoflurane and fentanyl to reach a value around 41 in the P group and 55 in the PK and K groups, this finding is supported by studies done by Bharti and Devrajan, Guignard and by Glass et al. regarding decrease in Bispectral index when using inhaled anesthetics and opioids [17–19].

After intubation, a rise in the BIS value was observed in the three groups, it was significantly higher in the KP and K group than in the P group but remained within the normal range needed during general anesthesia. Rise in BIS index usually occurs after intubation which is considered a noxious stimulus but it may be decreased by the use of inhalational anesthetics and opioids as demonstrated by Nakayama et al. and Ropcke et al. [20,21].

Regarding postoperative complication, apnea was defined as cessation of respiration for >30 s and occurred in 2 patients in the propofol group which were statistically insignificant relative to the other two groups. Several studies found different incidences of apnea while using propofol depending on the dose used, the rate of administration and the definition of apnea. In a study by Akin et al. in 2005, 6 out of 30 patients suffered from apnea when receiving propofol with a dose of 1.5 mg/kg) [10]. Regarding ketofol, apnea did not occur in any case which could be explained by the fact that the aforementioned potential side effect is dose-dependant, and when used in combination the doses administered of each can be reduced [10].

Mortero et al. [22] found that adding low-dose ketamine to propofol sedation attenuated the propofol-induced hypoventilation and preserved the integrity of airway (laryngeal and pharyngeal) reflexes and ventilatory response to carbon dioxide.

Regarding PONV, the antiemetic effects of propofol were evident in the mixture by reducing the number of patients who suffered from nausea and vomiting from 2 patients in the K group into no single patient in the KP group. This goes with the result of Willman and Andolfatto in 2007 [11] who studied ketofol (1:1 mixture of ketamine 10 mg/mL and propofol 10 mg/mL) administered intravenously to One hundred fourteen patients for procedural sedation and analgesia for primarily orthopedic procedures in emergency department and none of the patients suffered from vomiting in line with our results also Singh et al. [23], found no patients in their study suffered from nausea and vomiting.

The limitations of our conducted study is the small number of patients, however our results are encouraging regarding the use of such combination as a safe induction agent with minimal side effects. Also we should search for the optimal combination dosage of the two drugs used in the mixture.

7. Conclusion

Ketofol is a safe, effective alternative induction agent that lacks many side effects of its two components.

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