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Full Length Research Paper

A randomized double-blind controlled study of the efficacy of ketofol with propofol-fentanyl and propofol alone in termination of pregnancy

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The objectives of this study are to compare the effectiveness of different proportions of ketamine and propofol in ketamine-propofol single-syringe combination (ketofol), and to compare the effectiveness of ketofol with propofol-fentanyl and propofol alone in termination of pregnancy. Randomized, double-blind, controlled study of 100 female American Society of Anesthesiologists (ASA I or II) patients of age 18 to 40 years undergoing abortion was used. Patients were randomly divided into 5 groups of 20. Groups K21, K31, and K41 were given ketofol intravenously in the ratios of propofol:ketamine, 2:1, 3:1, and 4:1, respectively in small aliquots; group PF was given 1.5 to 2 mg/kg propofol and 50 mcg fentanyl, whereas group P was given only 2 mg/kg propofol. Blood pressure, heart rate, oxygen saturation; surgery, anesthesia, sedation, recovery, and discharge times were recorded. There was significant difference (P<0.05) in anesthesia, sedation, and discharge times. Group K21 had higher sedation, recovery, and discharge times than the other groups. All ketofol groups had high incidence of postoperative dizziness, whereas the non-ketofol groups had high incidence of intraoperative respiratory depression. Ketofol groups required less dosage of propofol than the non-ketofol groups with group P requiring the highest (3.5±0.6 mg/kg). Ketofol is as effective as propofol-fentanyl combination, especially in the ratios 3:1 and 4:1 (propofol:ketamine) for abortion.

Key words: Ketofol, ketamine, propofol, fentanyl, procedural sedation, abortion.

INTRODUCTION

The termination of pregnancy or abortion can be performed medically or surgically. Medical termination is achieved through drugs and it is effective till 49 days of gestation. Surgical termination can be done under local anesthesia if within 8 weeks of gestation or under procedural sedation and analgesia if above 8 weeks.

Ketofol is a combination of propofol and ketamine in a single syringe, and can be prepared in any desired concentration. Ketofol has been used for several years in procedural sedation and analgesia. It has been found to produce effective sedation and analgesia in gynecologic, ophthalmologic, orthopedic, and cardiovascular procedures in all age groups (Akin et al., 2005; Frey et al., 1999; Sharieff et al., 2007; Andolfatto and Willman 2010). The combination of propofol and ketamine has been found to oppose the hemodynamic and respiratory

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Abbreviations: HR, Heart rate; **NBP,** non-invasive blood pressure; **SBP,** systolic blood pressure; **DBP,** diastolic blood pressure; **SPO_2,** pulse oxygen saturation; **ECG,** electrocardiogram; ASA, American Society of Anesthesiologists; **Ketofol,** ketamine-propofol single-syringe combination; **ANOVA,** analysis of variance; **HSD,** honestly significant difference.

Table 1. Ramsay sedation scale.

Score	Response
1	Anxious or restless or both
2	Cooperative, orientated and tranquil
3	Responding to commands
4	Brisk response to stimulus
5	Sluggish response to stimulus
6	No response to stimulus

effects of each other. In combining these two drugs, the dose of each individual drug has also been highly reduced (Aouad et al., 2008; Andolfatto and Willman 2010). Thus, the propofol-ketamine admixture has been found to be very effective.

The abortion procedures are of very short duration (usually less than 15 min) and they just require analgesia and mild sedation. Ketofol has fast onset and good analgesic and sedative properties, thus making it ideal for such procedures. This study was designed as there has been no study comparing ketofol and propofol-fentanyl combination in abortion procedures.

MATERIALS AND METHODS

A hundred female patients of age group 18 to 40 years old and undergoing abortion in the First Hospital of Jilin University were enrolled in this study. These patients undergoing abortion had American Society of Anesthesiologists (ASA) physical status I or II. All patients were informed of the procedure and the anesthetic technique and an informed written consent was taken. All participants who met the eligibility criteria were recruited after signing an informed consent. Ethical approval for this study was granted by the First Hospital of Jilin University, Jilin, Changchun, China.

Patients with clinically significant cardiovascular, respiratory, and hepatic diseases and epileptic and psychiatric patients were excluded. Patient refusal and known hypersensitivity to the drugs were also excluded.

The following parameters were collected during the procedures at 3 to 5 min interval: heart rate (HR), non-invasive blood pressure (NBP), and pulse oxygen saturation (SpO_2). In addition to these parameters, electrocardiogram (ECG) and respiration were also monitored.

Patients were randomly divided (computer generated) into 5 groups with 20 patients each: K21, K31, K41, PF, and P. Patients in groups K21, K31, and K41 were given ketofol intravenously in the ratio of (propofol:ketamine) 2:1, 3:1, and 4:1, respectively in 1 to 5 ml aliquots as initial dose until adequate sedation was achieved. Ketofol for group K21 was prepared by adding 1 ml of 50 mg/ml ketamine to 10 ml of 10 mg/ml propofol. Ketofol for group K31 was prepared by adding 1 ml of 50 mg/ml ketamine to 15 ml of 10 mg/ml propofol. Ketofol for group K41 was prepared by adding 1 ml of 50 mg/ml ketamine to 20 ml of 10 mg/ml propofol. Ketofol was supplemented in 1 to 3 ml aliquots if required during the procedure. The PF group was given 1.5 to 2 mg/kg propofol and 50 mcg fentanyl, whereas the P group was given only 2 mg/kg propofol. Propofol (0.5 to 1 mg/kg) was repeated if required during the procedure for groups PF and P. The study was kept double-blind by one anesthesiologist preparing the drugs, while another administered them and the records were maintained by a resident.

The level of sedation was determined according to the Ramsay sedation scale (Table 1) and the time to sedation was recorded. A score of 5 or 6 on Ramsay sedation scale was required to begin the procedure. During the procedures, adverse events such as apnea, hypotension, hypoxia, myoclonus, seizure, rash, and airway intervention were recorded. Also, emergence phenomena like agitations, hallucinations, and vomiting after the procedure were recorded. Duration of surgery, duration of anesthesia, and the times to sedate, recover and discharge were also recorded. The duration of anesthesia is the time taken from the beginning of anesthesia to the time of recovery. The recovery time is taken as the time from the last dose of the anesthetic agent to the time taken for the patient to be conscious. The discharge time is the time from the recovery to the discharge to home. Patients were discharged if they did not have any headache, nausea or vomiting, and they had good respiration and could ambulate on their own.

Data were analyzed using Statistical Package of Social Sciences (SPSS) software and presented as mean ± standard deviation. The data were compared using one-way analysis of variance (ANOVA) test and post-hoc analysis for multiple comparisons within the groups was performed with Tukey's honestly significant difference (HSD) method. Kruskal-Wallis test was used to compare the adverse events between the different groups. P value of less than 0.05 was considered significant.

RESULTS

There was no significant difference ($P>0.05$) among age, weight, height, procedure duration, and recovery time in all groups, whereas anesthesia duration, sedation time, and discharge time had significant difference ($P<0.05$) (Tables 2 and 3). After post-hoc analysis using Tukey's HSD method, the mean difference in discharge time was found significant among different groups, whereas only groups P and PF had significant mean difference in anesthesia duration; and group K21 had significant mean difference in sedation time with the other groups. The procedure duration was slightly longer in group K41, while the anesthesia duration was slightly longer in groups K41 and P. The sedation, recovery, and discharge times were longer in group K21.

The average dose (Table 4) of propofol was the lowest in group K21 (1.6±0.3 mg/kg) and highest in group P (3.5±0.6 mg/kg). Among the ketofol groups, average dose of ketamine was the highest in group K21 (0.8±0.2 mg/kg) and lowest in groups K31 and K41 (0.6±0.1 mg/kg).

There was very high incidence of apnea in group PF (18/20) and hypoxia in group P (15/20). There was very high incidence of dizziness in the ketofol groups: 16 in K21 and K31 and 13 in K41. One patient each in groups K21 and K41 complained of headache (Table 5).

There were no significant changes ($P>0.05$) in the heart rates and baseline blood pressures in all the groups (Table 6). However, there were significant changes ($P<0.05$) in the after sedation and after recovery blood

Table 2. Demographic characteristics of different groups.

Characteristics	K21(n=20)	K31(n=20)	K41(n=20)	PF(n=20)	P(n=20)	P-value
Age (years)	27 ± 5	27.1 ± 4.5	25 ± 4.7	27.5 ± 4.6	26.4 ± 4.6	0.490
Weight (kg)	54.1 ± 8.1	57.6 ± 9.8	52.3 ± 7.8	54.2 ± 6.9	55 ± 6.2	0.327
Height (cm)	162.3 ± 4.9	162 ± 5.3	162 ± 6.1	162.4 ± 4.9	163.5 ± 3.7	0.889

Data are mean ± standard deviation (SD).

Table 3. Procedure, anesthesia, sedation, recovery and discharge times.

Parameter	K21 (n=20)	K31 (n=20)	K41 (n=20)	PF (n=20)	P (n=20)	P-value
PD (min)	6 ± 2.3	6.4 ± 2.1	7.3 ± 3.1	6.8 ± 1.9	6.9 ± 2.3	0.505
AD (min)	11.7 ± 3.7	10.6 ± 2.2	12.3 ± 3.6	9.8 ± 3.1	12.3 ± 3.6	0.018
ST (min)	0.8 ± 0.3	0.6 ± 0.2	0.6 ± 0.1	0.5 ± 0.1	0.5 ± 0.2	0.000
RT (min)	9.6 ± 3.9	7.8 ± 2.1	8 ± 2	7.7 ± 2.2	8 ± 2. 2	0.134
DT (min)	79.3 ± 20.8	62.5 ± 12.5	61 ± 14.3	45 ± 8.3	49.8 ± 6.8	0.000

PD: Procedure duration; AD: Anesthesia duration; ST: Sedation time; RT: Recovery time; DT: Discharge time. All times are in minutes.

Table 4. Average doses of drugs used in different groups.

Drug	K21 (n=20)	K31 (n=20)	K41 (n=20)	PF (n=20)	P (n=20)	P-value
Propofol (mg/kg)	1.6 ± 0.3	1.9 ± 0.4	2.4 ± 0.5	3 ± 0.6	3.5 ± 0.6	0.000
Ketamine (mg/kg)	0.8 ± 0.2	0.6 ± 0.1	0.6 ± 0.1	-	-	0.001
Fentanyl (mcg/kg)	-	-	-	0.9	-	-

P<0.05 considered as significant.

Table 5. Adverse events occurring in different groups.

Parameter	K21 (n=20)	K31 (n=20)	K41 (n=20)	PF (n=20)	P (n=20)	P-value
Apnea	0	0	4	18	3	0.000
Chin lift + O_2	0	2	0	2	15	0.000
Dizziness	16	16	13	0	2	0.000
Headache	1	0	1	0	0	0.553

Data presented as the number of patients. P<0.05 considered as significant.

pressures. Post-hoc analysis showed no significant mean difference in the after sedation systolic blood pressure (SBP), but there was significant mean difference in the after recovery SBP in PF with K21 and K31. There was also significant mean difference in the after sedation diastolic blood pressure (DBP) in K21 with K41 and PF, K31 with PF and after recovery DBP in PF with K21, K31, and K41. Two patients in group K41, four in group PF and two in group P had systolic blood pressure less than 90 mmHg after the initial dose of the drugs.

There was no bradycardia, hallucination, agitation or vomiting in any of the groups. All the patients did not have any recall of the procedure and also did not experience any pain during the procedure.

DISCUSSION

In this study, ketofol was as effective as propofol-fentanyl combination for abortion. We studied three concentrations of ketofol and they were all very effective for the procedure, but group K41 was the most effective. Groups K31 and K41 had similar sedation, recovery, and discharge times that were comparable to groups PF and P.

Group K21 had the lowest doses for each drug, but the

Table 6. Changes in vital signs in different groups.

Parameter		K21 (n=20)	K31 (n=20)	K41 (n=20)	PF (n=20)	P (n=20)	P-value
SBP (mmHg)	BL	110.5 ± 7.2	111.5 ± 10.1	106.1 ± 9.5	106 ± 8.7	108.4 ± 8.5	0.183
	AS	107.5 ± 9.5	106.9 ± 9.2	100.3 ± 10	99.1 ± 10.9	100.4 ± 8.7	0.011
	AR	113.5 ± 9.8	112.5 ± 9.8	109.85 ± 11	101.7 ± 10.5	106.3 ± 11.7	0.005
DBP (mmHg)	BL	73 ± 8.3	72.5 ± 9.2	68 ± 7.9	70.1 ± 7.2	69.9 ± 6 .6	0.249
	AS	70.9 ± 8.4	69.9 ± 8.1	63.4 ± 6.9	62.3 ± 9.1	64.2 ± 8	0.002
	AR	73.9 ± 7.2	71.8 ± 10.6	71.9 ± 9.1	61.9 ± 11	66.3 ± 10.4	0.001
HR (bpm)	BL	81.2 ± 10.8	85.55 ± 8.2	85.5 ± 13	78.9 ± 14.2	83 .7 ± 10.9	0.304
	AS	79.7 ± 11.9	80.8 ± 10.2	84.2 ± 10.1	76.1 ± 9.1	82.5 ± 1	0.171
	AR	84.7 ± 11.8	87.3 ± 11	81.8 ± 7	84.9 ± 15.5	87.7 ± 10.9	0.487

SBP: Systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; BL: baseline; AS: after sedation; AR: after recovery. P<0.05 considered as significant.

incidence of postoperative dizziness was high. The sedation, recovery, and discharge times were also longer in this group. Group K31 had higher dose of propofol, but lower dose of ketamine than group K21. This group had very few incidence (n=2) of respiratory depression and high incidence of postoperative dizziness, but the sedation, recovery, and discharge times were shorter than group K21. Group K41 had the highest dose of propofol and the lowest dose of ketamine among the ketofol groups. This group had few incidence (n=4) of respiratory depression and relatively lower incidence of postoperative dizziness than the other ketofol groups. The sedation, recovery, and discharge times were also shorter than the other ketofol groups; but they were slightly longer than groups PF and P. Groups PF and P used higher doses of propofol and had higher incidences of respiratory depression than the ketofol groups, but had few or no postoperative dizziness. The sedation, recovery, and discharge times of group p were also shorter than the ketofol groups. However, group P required significantly higher dose of propofol since no analgesic was used.

There have been numerous studies regarding the stability and effectiveness of ketofol, especially in the emergency department as an agent for procedural sedation and analgesia. Ketofol solutions have been found to be stable up to 3 h when stored at room temperature with exposure to light in 50:50 and 30:70 proportions (Donnelly et al., 2008).

Several studies have been performed comparing the efficacy of ketofol to propofol and to propofol-fentanyl combination and have found ketofol to be very effective. In the studies comparing ketofol to propofol, Akin et al. (2005) found that some patients in the propofol group needed ventilatory support and the onset of sedation was faster in the ketofol group. Thus, they concluded that the addition of ketamine to propofol decreased the respiratory depression and produced faster onset of sedation. In the study comparing propofol-ketamine to propofol-fentanyl combination for endometrial biopsy, Akin et al. (2005), found that the ketofol group had more respiratory depression and the time to discharge was longer due to adverse events, such as nausea, vertigo, and visual disturbances (Akin et al., 2005). However, the time to recover was similar in both groups. Similarly, other studies have also found ketofol to be as effective as and even safer than propofol-fentanyl combination (Goh et al., 2005; Messenger et al., 2007).

The efficacy of ketofol at 1:1 and 4:1 (propofol:ketamine) was studied by Daabis et al. (2005). They found that ketofol at 4:1 concentration provided adequate sedation and analgesia without hemodynamic and respiratory depression or psychotomimetic side effects for procedural operations. Badrinath et al. (2000) published a study of one hundred female outpatients undergoing breast biopsy procedures under local anesthesia with an infusion of propofol in combination with different doses of ketamine. They reported that the combination of propofol and ketamine at 5:1 concentration provides effective sedation and analgesia during monitored anesthesia care.

We believe that in our study the duration of the procedures was very short (up to 7 min) which probably led to the higher recovery and discharge times and also the higher incidence of postoperative dizziness among the ketofol groups. However, the intraoperative respiratory depression was nil or significantly less in the ketofol groups.

Conclusion

Although, there has not been many studies regarding the

use of ketofol, it has been found to be very effective for procedural sedation and analgesia. There have been very few adverse events associated with the use of ketofol as the ketamine and propofol counteract the hemodynamic disturbances and respiratory effects of each other. Different proportion of the ketamine and propofol can be used according to the type and duration of the surgery.

We can conclude from our study that ketofol in the ratios 3:1 and 4:1 (propofol:ketamine) are as effective as the propofol-fentanyl group for abortion. The ketofol groups had few intraoperative events, but higher postoperative events, whereas the propofol-fentanyl group had high intraoperative events, but no postoperative event.

REFERENCES

Akin A, Esmaoglu A, Guler G, Demircioglu R, Narin N, Boyaci A (2005). Propofol and propofol-ketamine in pediatric patients undergoing cardiac catheterization. Pediatr Cardiol. 26:553-557.

Akin A, Esmaoglu A, Tosun Z, Gulcu N, Aydogan H, Boyaci A (2005). Comparison of propofol with propofol-ketamine combination in pediatric patients undergoing auditory brainstem response testing. Int. J. Pediatr. Otorhinolaryngol. 69:1541-1545.

Akin A, Guler G, Esmaoglu A, Bedirli N, Boyaci A (2005). A comparison of fentanyl-propofol with a ketamine-propofol combination for sedation during endometrial biopsy. J. Clin. Anesth. 17:187-190.

Andolfatto G, Willman E (2010). A prospective case series of pediatric procedural sedation and analgesia in the emergency department using single-syringe ketamine-propofol combination (ketofol). Acad. Emerg. Med. 17:194-201.

Aouad MT, Moussa Ar, Dagher CM (2008). Addition of ketamine to propofol for initiation of procedural anesthesia in children reduces propofol consumption and preserves hemodynamic stability. Acta Anaesthesiol. Scand. 52:561-565.

Badrinath S, Avramov MN, Shadrick M, Witt TR, Ivankovich AD (2000). The use of ketamine-propofol combination during monitored anesthesia care. Anesth. Analg. 90:858-862.

Daabiss M, Elsherbiny M, AlOtibi R (2009). Assessment of different concentrations of ketofol in procedural operation. Br. J. Medical. Practitioners 2:27-31.

Donnelly RF, Willman E, Andolfatto G (2008). Stability of ketamine-propofol mixtures for procedural sedation and analgesia in the emergency department. Can. J. Hosp. Pharm. 61:426–430.

Frey K, Sukhani R, Pawlowski J, Pappas AL, Mikat-Stevens M, Slogoff S (1999). Propofol versus propofol ketamine sedation for retrobulbar nerve block: comparison of sedation quality, intraocular pressure changes, and recovery profiles. Anesth. Analg. 89:317-321.

Goh PK, Chiu CL, Wang CY, Chan YK, Loo PL (2005). Randomized double-blind comparison of ketamine-propofol, fentanyl-propofol and propofol saline on haemodynamics and laryngeal mask airway insertion conditions. Anaesth. Intensive Care 33:223-228.

Messenger DW, Murray HE, Dungey PE, VanVlymen J, Sivilottin MLA (2007). Low-dose ketamine versus fentanyl as adjunct analgesic to procedural sedation with propofol: a randomized clinical trial. Can. J. Emerg. Med. 9:183.

Sharieff GQ, Trocinski DR, Kanegaye JT Fisher B, Harley JR (2007). Ketamine-propofol combination sedation for fracture reduction in the pediatric emergency department. Pediatr. Emerg. Care 23:881-884.