Original article

A comparative study of ketofol and fentafol for evacuation of retained products of conception (ERPC)

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Abstract

Background: Intravenous balanced anesthesia (IVA) is desirable during the evacuation of retained products of conception (ERPC) to avoid the use of inhalational anesthetics agents that may cause uterus relaxation, the possibility of bleeding, and the risk of uterus perforation.

Objectives: The aim of this study was to compare the efficacy and safety of ketofol (a mixture of propofol and ketamine) versus fentafol (a mixture of propofol and fentanyl) during the ERPC.

Methods: A double-blind, randomized comparative study was conducted among a total of 60 women of childbearing age categorized as grades I and II according to the American Society of Anesthesiologist (ASA), presented for ERPC. The patients were selected and randomized blindly into two groups (K group and F group), with 30 patients in each group. The K group was given ketofol (1ml containing 5mg of propofol and 5mg of ketamine) and F group was given fentafol (1ml containing 5mg propofol and 5mcg fentanyl). An intravenous loading dose of ketofol or fentafol was given slowly, with doses ranging from 1ml to 2ml/10kg, to reach level 5 or 6 of the Ramsay Scale of Sedation (RSS), followed by small incremental doses which were given when RSS dropped to 4. Hemodynamic parameters, success, and side effects were assessed throughout the procedures.

Results: K group demonstrated a significant increase in heart rate (HR) and blood pressure (BP), compared to significant decreases in the F group. Decreases in oxygen saturation (SpO_2) and respiratory rate (RR) were observed more in the F group. However, no patients developed hypertension, hypotension, apnea, hypoxemia or serious adverse effects. Ketofol showed less propofol consumption and a short recovery time.

Conclusions: Both ketofol and fentafol offer optimum conditions for ERPC. Ketofol is characterized by more stable hemodynamic parameters, a smaller dosage and faster recovery. [*Ethiop.J. Health Dev.* 2019; 33(2):88-93]

Key words: Propofol, ketamine, fentanyl, retained products of conception (RPC), ketofol, fentafol

Background

Evacuation of Retained Products of Conception is a common procedure among women of childbearing age worldwide. Most of the cases present with anxiety and other psychological disorders related to their loss of fetus and associated vaginal bleeding, especially with recurrent abortions. These factors may increase the pain associated with the procedure. Consequently, anesthesia plays a major role during ERPC. The choice of anesthesia will be affected by certain considerations, including availability, effectiveness, safety, side effects, practitioner's choice, cost, and women's preferences (1). It could be performed under local, regional, sedation/analgesia and general anesthesia (GA) (2,3). Due to the complications of GA, many practitioners try to avoid it. Sedation/analgesia may be a good choice, and many different combinations can be used. Ketofol and fentafol are simple, safe and low cost, and could be used effectively, especially in developing countries. Because ketofol and fentafol cause no issues with airway patency, there is little need for airway instrumentation. A small total dose of propofol and ketamine or fentanyl is utilized to achieve a satisfactory level of sedation/analgesia. This is accompanied by few adverse events and residual anesthetics, leading to early ambulation and discharge. Ketofol utilization for emergency department procedural sedation/analgesia is efficacious (4,5). Both propofol-ketamine and propofol-fentanyl combinations are found to be rapid, pleasant and safe during the induction and maintenance of total intravenous endotracheal intubation GA, with only a few unpleasant side effects and only minor hemodynamic effects (5).

New applications have been developed to administer ketamine involving small doses, either alone or in combination with other anesthetic agents. Nowadays, it is used extensively in anesthesia, palliative care, intensive care, and procedural sedation for both adults and children (5,6). Propofol has antiemetic, anxiolytic and antipruritic effects. It is characterized by rapid induction and recovery, which makes its use preferable during day case surgery (7,8). Fentanyl, a lipid-soluble opioid, has a rapid onset and short duration of action, with potent properties. Fentanyl has been available for more than 50 years. Even with new potent, safer, and faster onset generations of the drug, it remains popular and is used extensively. It has a minimal cardiovascular effect and does not cause histamine release (9,10). In our study, we have aimed to compare the efficacy and safety of ketofol (a mixture of propofol and ketamine) with fentafol (a mixture of propofol and fentanyl) during the ERPC. The secondary objective was to assess and compare ketofol- and fentafol-related complications.

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Material and methods

This double-blind, randomized comparative study was conducted in Soba University, Ibrahim Malik, and Academic Charity Hospitals, Khartoum, Sudan from early June to late August 2016. Ethical approval was obtained from the ethical committee of Soba University Hospital, College of Medicine at Khartoum University. Permission was obtained from the authorities at each of the hospitals. A total of 60 patients of childbearing age who presented with incomplete abortion for ERPC were enrolled in the study, including those classified as ASA class I: healthy, non-smoking, no or minimal alcohol use; and ASA class II: mild diseases only without substantive functional limitations. Exclusion criteria included patients with hypertension, hypotension, hepatic or renal diseases, difficult airways, known hypersensitivity to propofol, ketamine or fentanyl, full stomach or need for rapid sequence intubation, mental illnesses and psychiatric conditions. Also, patients unwilling to participate were excluded from the study.

All patients were informed, and written consent was obtained. Preoperative assessment and evaluation for every patient were done as per normal procedures. Investigations and a fasting regimen were followed as routine. Patients were randomly assigned to one of two groups, K or F group, 30 patients in each, using a computer-generated block randomization program. The results of the selection process were kept in an opaque envelope and an assigned person allocated each patient accordingly to one of the groups. K group received the ketofol, a mixture of propofol and ketamine via a 20ml syringe, in a 1:1 ratio (1ml containing 5mg propofol and 5mg ketamine), while F group was given fentafol, a mixture of propofol and fentanyl in a 20ml syringe, with 1ml containing 5mg propofol and 5mcg fentanyl. These were prepared by an anesthesia technician and were concealed from both the assigned anesthetist and the one who administered them. There were no visible differences in appearance between the two mixtures. All patients were pre-medicated with ondansetron 4mg and glycopyrrolate 0.2mg intravenously.

In the operation room, patients were connected to standard equipment to monitor heart rate, electrocardiograph (ECG), SpO_2, respiratory rate, and noninvasive blood pressure before the drugs were administered. Monitoring was continued throughout the procedure and in the post-anesthesia care unit (PACU). An intravenous cannula was secured, and ringer lactate fluid was started. Supplemental oxygen via nasal cannula with a flow rate of 4L/minute was given to all patients. All resuscitation drugs and equipment were ready. Drugs were administered by the anesthetist in charge, with a person assisting and another one for monitoring of the patients. Ketofol or fentafol were given slowly with doses ranging from 1 to 2 ml/10 kg until an optimum level of sedation was reached. The operation started at 5 or 6 levels as per RSS (Table 1). Incremental doses depended on clinical signs and RSS, and were given when RSS dropped to 4. Recordings of the cardiorespiratory parameters were made every 5 to 15 minutes. Needs for airway management and rescue analgesia were recorded. All patients were given 10 units of syntocinon infusion in 500ml normal saline near the end of the procedure. During the procedure and postoperatively, complications such as nausea, vomiting, shivering, hallucination, delirium and bad emergence phenomena were recorded. The end of monitoring and discharge of the patient from PACU followed a return to the baseline level of consciousness, protective reflexes, and when SpO_2 was greater than 92% on room air.

Data entry and analysis using the Statistical Package for Social Sciences (SPSS version 21.0) was performed. The categorical data are presented as numbers and percentages, and were subjected to Chi-square test for analysis, while the parametric data are presented as mean and standard deviation and were subjected to ANOVA test. The statistical significance was considered at P-value ≤ 0.05.

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

Results

Table 2 shows the demographic characteristics, while Table 3 shows the intraoperative effects of ketofol and fentafol on the patients' HR, BP, RR, and SpO_2.

Table 2: The demographic characteristics of both groups

	K group (n = 30)	F group (n = 30)	P-value
Age			
Range	21-43	20-45	
Mean ± SD	30.90±5.60	32.17±6.54	0.422
Body weight	76.93±10.27	76.67±13.81	0.934
ASA			
I	24 (80%)	25 (83.3%)	0.743
II	6 (20%)	5 (16.7%)	
Gravidity			
1	7	5	
2	6	7	
3	6	8	
4 and more	11	10	
The mean duration of operation	23.40±5.69	25.07±6.30	0.286

K = Ketofo; F = Fentafol

Data was expressed as a mean ± SD, numbers and percentages (ANOVA test).

Table 3: The mean of the baseline and intraoperative parameters in both groups

	K group (n = 30)	F group (n = 30)	P-value	K group (n = 30)	F group (n = 30)	P-value
	Baseline			**Intraoperative**		
Systolic blood pressure	120.70±6.90	121.97±8.17	0.518	132.27±3.96	116.67±6.42	**<0.001**
Diastolic blood pressure	75.53±6.43	75.73±7.24	0.910	82±6.37	69.53±7.15	**<0.001**
Mean arterial blood pressure	90.43±4.44	90.70±6.59	0.853	98.67±3.78	85.27±5.82	**<0.001**
Heart rate	79.33±8.29	78.53±8.69	0.717	87.23±7.50	69.50±7.14	**<0.001**
Oxygen saturation	97.17±0.95	97.50±0.73	0.137	96.47±1.01	95.40±1.04	**<0.001**
Respiratory rate	15.67±1.15	15.43±1.10	0.412	12.57±1.30	12.17±1.21	0.222

Data was expressed as a mean ± SD (ANOVA test).

Patients in the K group had an increase in HR from the baseline (79.33±8.29 to 87.23±7.50), while the F group showed a decrease (from 78.53±8.69 to 69.5±7.14) (highly significant P-value).

The systolic BP in K group increased from 120.70±6.90 preoperatively to 132.27±3.96 intraoperatively, while in F group it decreased from 121.97±8.17 to 116.67±6.42 (highly significant P-value). The diastolic BP increased in K group from the preoperative level of 75.53±6.43 to 82±6.37 intraoperatively, while it dropped in F group (75.73±7.24 to 69.53±7.15) (P-value <0.001 in both). The mean arterial pressure (MAP) of K group increased from 90.43±4.44 to 98.67±3.78, while in F group it decreased from 90.70±6.59 to 85.27±5.82 (highly significant P-value).

Intraoperatively, SpO_2 dropped from 97.17±0.95 to 96.47±1.01 in K group. In F group, there was a greater drop, from 97.50±0.73 to 95.40±1.04 (highly significant P-value).

The intraoperative difference in the RR between the two groups was found to be insignificant. However, there were decreases in intraoperative RR from the baseline in both groups. In K group, it decreased from 15.67±1.15 to 12.57±1.30, while in F group it decreased from 15.43±1.10 to 12.17±1.21 (highly significant P-value in both).

However, there are no clinical significances, as none of the patients developed hypertension, hypotension, apnea, or hypoxemia. Also, no patient developed vomiting or movement that could interfere with the operation.

Table 4 shows the postoperative effects of ketofol and fentafol on patients' HR, BP, RR, and SpO_2, postoperatively.

Table 4: The mean of postoperative parameters for both groups

	K group (n = 30)	F group (n = 30)	P-value
Systolic blood pressure	124.83±6.41	119.60±7.20	0.004
Diastolic blood pressure	78.20±6.58	74.50±6.77	0.036
Mean arterial blood pressure	93.73±4.27	89.53±5.61	0.002
Heart rate	81.90±6.52	77.73±7.81	0.029
Oxygen saturation	98.90±0.92	97.80±1.37	0.001
Respiratory rate	13.97±0.96	13.50±1.14	0.089

Data was expressed as a mean ± SD (ANOVA test).

Postoperatively, systolic BP in K group decreased to 124.83±6.41, while in F group it increased to 119.60±7.20, with a significant P-value. The diastolic BP in the K group decreased to 78.20±6.58, while in F group it increased to 74.50±6.77. The difference is marginally significant (P-value 0.036). The MAP in the K group decreased to 93.73±4.27 and in the F group increased to 89.53±5.61 (P-value 0.002).

The HR of group K and group F were 81.90±6.52 and 77.73±7.81, respectively (significant P-value). The postoperative difference of SpO_2 between the two groups was significant (98.90±0.92 in K group and 97.80±1.37 in F group) (P-value 0.001).

Table 5 shows the adverse events, needs for airway management, rescue analgesia, and sedative agents for both groups.

Table 5: The adverse events, needs for airway management, rescue analgesia, and sedative agents for both groups

	K group (n = 30)	F group (n = 30)	P-value
Adverse events			
Hypoxemia	0	0	
Apnea	0	0	
Vomiting	0	0	
Nausea	0	1	0.320
Delirium, nightmares	0	0	
Hallucination	2 (6.57%)	0	0.156
Need for airway alignment			
Head tilt or chin lift	2	3	0.224
Jaw thrust	0	0	
Need for airway instrumentation			
Basic	0	0	
Advanced	0	0	
Need for rescue analgesia	0	0	
Need for sedative agents	2 (6.57%)	0	0.156

Data is expressed as numbers and percentages. P < 0.05 is significant (Chi square test).

There were no instances of hypoxemia, apnea, vomiting, delirium, or nightmares. One patient from F group experienced mild self-limiting nausea. Two patients from K group had a mild form of hallucination, which was treated effectively by small dose of intravenous midazolam (P-value 0.156). Head tilt or chin lift was needed in two patients in K group compared to three patients in F group (P-value 0.224). Airway instrumentation was not recorded. No rescue analgesia was needed in PACU.

Table 6 shows the propofol consumption, procedure duration, sedation time, and time from last dose to full recovery.

Table 6: Propofol consumption, procedure duration, sedation time, and time from last dose to full recovery

	K group (n = 30)	F group (n = 30)	P-value
Propofol consumption	100.67±19.86	112.50±21.76	0.032
The mean duration of operation	23.40±5.69	25.07±6.30	0.286
Sedation time	35.40±5.45	39.07±6.20	0.018
Time from last dose to full recovery	14.10±2.55	16.90±2.73	<0.001

Data was expressed as a mean ± SD (ANOVA test).

There was no statistical difference in the mean duration of procedure between the two groups. Sedation time in K group was lower than F group (significant P-value 0.018).

The mean of the total dose of propofol was higher in the F group compared with the K group, with significant difference (P-value 0.032). Time from the last dose to full recovery was higher in F group compared with K group (highly significant P-value <0.001).

Discussion

IVA is desirable during ERPC to avoid the use of inhalational anesthetic agents, which may cause relaxation of the uterus, resulting in more bleeding and the risk of uterus perforation during the procedure. Both ketofol and fentafol can provide an optimum sedation/analgesia for many minor surgical procedures, including ERPC. In each mixture, one drug will counteract the most severe disadvantages of the other.

Kestin *et al.* evaluated anesthesia for ERPC among 44 patients. They compared alfentanil plus etomidate and fentanyl plus thiopentone with 70% nitrous oxide in oxygen. They report a higher rate of return of higher mental function in the alfentanil-etomidate technique. However, it was associated with significantly more pain on injection and a higher frequency of postoperative vomiting (40%) (11). Jakobsson *et al.* studied four different combinations of IVA in patients who underwent termination of pregnancy under GA. The patients were randomly allocated to receive one of four anesthetic combinations; (1) propofol-ketamine 20mg, (2) propofol-fentanyl 0.1mg, (3) thiopentone-fentanyl 0.1mg, (4) methohexitone-fentanyl 0.1mg. All combinations offered good conditions to perform the procedure for termination of pregnancy. However, the propofol-fentanyl combination was found to be the best in regards to hemodynamic stability (12).

Following intravenous administration of fentanyl, its analgesic effect will occur within one to two minutes. It is 100 to 200 times more potent than morphine. Despite the minimal cardiovascular effects of fentanyl and lack of plasma histamine release, a decrease in HR and BP may occur (10).

Our study revealed good hemodynamic stability, with marginal superiority of ketofol. No patient in the ketofol group developed clinical tachycardia or hypertension. Fentafol was associated with more drops in HR and BP. However, these drops, clinically, were insignificant, as neither bradycardia nor hypotension occurred. This finding is similar to Bajwa *et al*., who found a slight decrease in HR (9%) with fentanyl-propofol compared to an increase in the propofol-ketamine group. Also, the BP fall in the fentanyl-propofol compares with a slight increase in the propofol-ketamine group (5). In a study on ketofol in the ER for procedural sedation/analgesia, Willman *et al.* report only a few adverse events, which were either self-limiting or responded to minimal interventions (13). Also, another study of ketofol for painful minor operations shows stable hemodynamic parameters, with no clinical tachycardia or hypertension (14).

In our study, most patients maintained their airway. No patient needed either basic or advanced airway support. No patient developed hypoxia or apnea. Some patients needed only airway alignment in the form of head tilt or chin lift, while jaw thrust was rarely used. The lowest SpO_2 recorded was 94% in the F group. The greatest decrease in the RR was with fentafol. However, no RR less than 10/min was recorded. Bajwa *et al.* state no difference in SpO_2 between ketofol and fentafol. This may be because the patients in that study were intubated. However, they recorded a better recovery ventilation score in the propofol-ketamine group (5). Willman *et al.* report transient hypoxia in three patients (2.6%) during ketofol procedural sedation/analgesia among a cohort of 140 patients. One patient (0.9%) required bag-valve mask ventilation. Four patients (8.7%) required repositioning for airway malalignment. No patient needed endotracheal intubation (13). Sharma *et al.* report more respiratory depression with fentafol. However, only simple maneuverings were required to solve the airway mal-alignments (15). In another study, ketofol presented a few airway complications, which were resolved by the same simple technique (14).

As propofol lacks analgesic properties, it cannot be used as a sole agent to provide anesthesia. The dose used alone to prevent patient movement may cause significant impairment of cardio-respiratory function. The adding of narcotic could decrease the required dose of propofol, but may result in cardio-respiratory depression (16). Kb *et al.* compared propofol and ketamine versus propofol and fentanyl for puerperal sterilization. They noticed more intraoperative respiratory depression, airway obstruction, and apnea with fentafol. Co-administration of low-dose ketamine is known to produce positive mood effects and enhance early recovery. While ketamine preserves airway patency, the addition of propofol may abolish the unwanted side effects of ketamine (16). Prakash *et al.* compared three different concentrations of propofol-ketamine and propofol-fentanyl, in a sample of 60 adult females, scheduled for elective day care gynecological procedures. Patients had received a slow bolus injection followed by small aliquots of ketamine-propofol (1:1) (group A), ketamine-propofol (1:2) (group B), and fentanyl-propofol (group C). No differences in hemodynamic stability were recorded (17).

No patient, in our study developed postoperative vomiting, delirium, nightmares or headaches. However, one patient from F group experienced mild nausea, which was self-limiting. Two patients in the K group had a mild form of hallucination in the postoperative period, treated by a small dose of intravenous midazolam with immediate response. These may have been due to the small doses we used. Also, a high dose of ketamine may increase the occurrence of nausea and vomiting (16). In the study of ketofol by Willman and Andolfatto, three patients (2.6%) had mild unpleasant emergence, of whom one (0.9%) received midazolam (13). Perumal *et al.* support the effectiveness of midazolam premedication in attenuation of the postoperative emergence phenomenon related to ketamine anesthesia (18).

In this study, the mean of the total dose of propofol was higher in fentafol. Time from the last dose to full recovery was found to be shorter in the K group. The median recovery time reported by Willman and Andalfatto was 15 minutes (13). Sharma *et al*. demonstrate asmaller dose of propofol consumed in the ketofol (15). Different studies of propofol–ketamine or propofol–fentanyl show smooth recovery with minimal residual effects (5,13-15). During the whole stay in the PACU, none of the patients demonstrated any need for rescue analgesia.

Conclusions

Both ketofol and fentafol offer safe, effective and optimum sedation/analgesia for ERPC. Ketofol is characterized by more stable hemodynamic parameters, smaller dose and faster recovery time. For these reasons, ketofol showed superior advantage over fentafol and should be recommended during the ERPC sedation/analgesia procedure. Even with safety and the absence of serious adverse events, feasible and tight monitoring is still recommended.

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