Reliable and rapid smooth extubation after Ketofol for induction of general anesthesia in Laparoscopic Drilling of polycystic ovary: A randomized controlled trial.

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Research article

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Abstract

Background : the outcome of ketofol on the hemodynamics and the airway response during induction of general anesthesia has been studied before. Its effect on the smoothness of extubation has not been studied before. So, we aimed to assess the effect of ketofol on the smoothness of extubation and compare it with propofol only for the induction of general anesthesia.

Methods: This double-blind, randomized, and controlled study was conducted on one hundred and six American Society of Anesthesiologists Physical status "ASA PS" class I and II female patients aged 18-40 years old and scheduled for laparoscopic drilling for polycystic ovary disease under general anesthesia. The patients were assigned into one of two groups (53) patients each; group KP = ketofol and group P = propofol.

Results: There was a good sedation score during suction and extubation in the ketofol group. Airway response and smoothness of extubation were better in the ketofol more than the propofol group.

Conclusion: Ketofol as an induction anesthetic agent was effective in attenuating the airway response during extubation more than profofol only.

Trial registration: This trial was retrospectively registered at the Clinical Trial.gov with the Identification Number: NCT04365686.

Background

Tracheal extubation is a critical and stressful moment during general anesthesia at which many hazardous and unwanted hemodynamics and airway responses may occur such as tachycardia, hypertension, dysrhythmias, coughing, laryngospasm, and bronchospasm ([1, 2]).

These hazardous responses are ought to the sudden release of catecholamines during tracheal extubation [3]

Many medications have been studied to reduce the stress response during extubation aiming for the achievement of a state of smooth extubation such as including intravenous lignocaine, short-acting opioids as fentanyl, remifentanil, esmolol, endotracheal local anesthetic instillation, and dexmedetomedine. [4-9]

Propofol (2, 6-diisopropyl phenol) is a sedative and hypnotic drug with antiemetic property used for induction and maintenance of general anesthesia and in the intensive care units (ICU) for sedation. It produces its effect by facilitation of inhibitory neurotransmission mediated by GABA (Gama Amino Butyric Acid) depression [10- 12]

Ketamine is a phencyclidine derivative used for the induction of general anesthesia. It has favorable analgesic and amnestic properties but increases sympathetic activity, nausea, vomiting, and undesirable

psychomimetic disorders. [13, 14]

Ketofol (ketamine-propofol mixture) as an induction agent drug and its effect on hemodynamics has been studied previously. [15, 16] Its effect on the airway responses during induction of anesthesia was studied by Aberra et al. [17]

We hypothesized that giving ketofol as an induction agent getting the beneficial effects of both medications would favorably affect both the hemodynamics and the airway response during extubation. This study aimed to compare the effect of injecting a single dose of ketofol versus propofol on the smoothness of extubation as regards the airway response and the hemodynamics when given for the induction of general anesthesia in laparoscopic drilling of polycystic ovary disease.

Methods

Following ethical committee approval and research is coded (R83) of Anesthesia Department, Fayoum University and obtaining written informed consent, this study was conducted on one hundred and six American Society of Anesthesiologists Physical Status "ASA PS" class I and II female patients aged above 18 years old up to 40 years old and scheduled for laparoscopic drilling for polycystic ovary under general anesthesia. This trial protocol was registered at the **Clinical Trial.gov with the Identification Number: NCT04365686.** This study was conducted in El Fayoum University Hospitals and took 12 months between April 2019 and April 2020. Patients suffering from cardiac, hepatic, renal diseases, history of epilepsy were excluded from this study. The patients were randomly allocated by a computer-generated table into one of the two study groups. The randomization sequence was concealed in opaque sealed envelopes. The envelopes were opened by the study investigators just after recruitments and admission to the operation room. Only assessors and data collectors were blinded to the group's allocations. Our study adheres to the CONSORT guidelines.

The two study groups of this randomized, double-blind and parallel clinical trials are Group KP (Ketofol group): includes fifty-three female patients who received propofol (1mg/kg) plus ketamine (0.5mg/kg) at the induction of general anesthesia and Group P (propofol group): includes fifty- three female patients who received propofol (2mg/kg) only at the induction of general anesthesia.

After securing intravenous access by a 20g i.v. cannula, intravenous premedication (midazolam 2 mg and 4mg ondansetron) was administered to all patients. Standard ASA monitoring (5-lead ECG, noninvasive blood pressure (NIBP), and pulse oximetry) was applied to all the patients for the recording of heart rate (HR), NIBP, and oxygen saturation by a multi-parameter monitor. Induction of general anesthesia was achieved as follows: in Group KP (Ketofol group), fifty-three female patients received propofol (1mg/kg) plus ketamine (0.5mg/kg) at the induction of general anesthesia while in Group P (Propofol group), fifty-three female patients received propofol (2mg/kg) only at the induction of general anesthesia.

Patients in both groups received intravenous fentanyl 2 µg/kg, and atracurium 0.5 mg\kg. After tracheal intubation, general anesthesia was maintained by isoflurane 1.5 % in 2 L/min oxygen-air mixture 50 %:50 % and atracurium 0.1 mg/kg every 30 minutes, if needed. At the end of the surgery, inhalational anesthesia was stopped and reversal of the neuromuscular blockade was done by intravenous neostigmine 0.05mg/ kg and atropine 0.01mg/kg.

Hemodynamics [HR and mean arterial blood pressure (MAP)] were assessed at 5 minutes interval from the time of reversal of muscle relaxant (about five miutes before the expected time of extubation) up to 20 minutes after extubation. The level of sedation during oral suction and extubation was assessed using observer assessment sedation score (Table: 1) and the airway response under direct laryngoscopy to oral suction was noted by five-point scale (Table 2). [18] After 5 minute interval, the level of sedation and smoothness of extubation was noted by four-point scale (Table: 3). [18]

Our primary outcome was the assessment of smoothness of extubation while, our secondary outcomes were assessment of airway response to laryngoscopy and suction, sedation score, and hemodynamics as mentioned before.

Sample size calculation

Based on our pilot study, that was done on thirty patients who were randomly allocated by blind envelope methods into two groups ten patients each. These patients were not included in the final study. The Sample size was calculated (G* power version 3.0.10). The minimal sample size was calculated to be 48 patients in both groups needed to get the power level of 0.80, an alpha level of 0.05 (two-tailed), an effect size of 0.58 for grading of smoothness of extubation grade 1 (mean ± SD) in the study group and the control group only is (1.5 ± 0.8) and (2.0 ± 1.2) respectively. Based on the results of the pilot study to overcome the problem of loss of follow up, the calculated sample size was increased by 10% to reach 53 in each group.

Statistical analysis

Statistical analysis was done SPSS for Windows software version 23. Descriptive statistics were done for categorical variables and presented as numbers and percentages. While for numerical data, descriptive statistics were done the mean and the standard deviation being normally distributed. The Independent t-test was used to compare numeric variables in the two groups being either normally distributed data or based on the central limit theorem. Chi-Square test to analyze the difference in the extubation quality, the sedation score, and the adverse events. ***P*** value< 0.05 was considered as statistically significant.

Results

A total of 106 patients participated in this study. They were randomized into the K group (53 patients) and the P group (53 patients). All the patients completed the study and there were no dropouts (Fig:1). There were no statistically significant differences between the two study groups as regards the

demographic data, duration of surgery, duration of anesthesia and postoperative pethidine consumption except for the clinically insignificant height (Table: 4).

Hemodynamic parameters (MAP and HR) 5 min before extubation, at extubation, and every 5 min later till 20 minutes post-extubation are detailed in (Table:5) and (Figures:2and 3).

The MAP was significantly higher in the P group than in the KP group at all the readings except at 5 min after extubation where the difference was non-significant (Table: 5) and (Figure:2).

HR was lower in the KP group than in the P group at all reading times and that difference was statistically significant (Table: 5) and (Figure:3).

The grade of smoothness of extubation, our primary outcome, was 1 in all cases of the KP group and the grade was 2 to 4 for the cases of the P group. The relationship is highly significant and the Somers' D value = 1 meaning that there is a perfect trend association (Table: 6) and (Figure: 4).

The level of sedation during the suction process was 1 in 83% of the KP group cases with lower numbers at levels 2 and 3. While in the P group, it was at a level of 1 in19% of the cases whereas, the rest of the cases were at levels of 2 and 3. This relationship is highly significant and the Somers' D value = 0.67 meaning that there is a strong trend association (Table: 6).

The grade of airway reflex was 2 in 11 cases (20.8%) and 3 in 33 cases (62.3%) of the KP group cases with lower numbers at grades 4 and 5. While in the P group, 12 cases (22.6%) of the cases were in grade 2 and 33 cases (62.3%) in grade 4. Also, this relationship is highly significant and the Somers' D value = 0.55 meaning that there is a strong trend association (Table: 6).

The level of sedation at extubation was 5 in all cases of the P group whereas; it was at the level of 2 and 3 for the cases of the KP group. The relationship is highly significant and the Somers' D value = 1 meaning that there is a perfect trend association (Table: 6).

Discussion

Stress response during extubation is an unwanted and unpredictable response that makes anesthesiologists vigilant and attentive for minimizing its effect on hemodynamics and airway reflexes.

In our study, we compared the effect of injecting a ketofol compared to propofol at the induction of general anesthesia on the smoothness of extubation as regards airway response and hemodynamics in laparoscopic drilling of polycystic ovary disease.

Aboeldahab et al studied the effect of ketofol compared to its two constituents as an induction agent in 60 patients undergoing hernia repair under general anesthesia. [15] They examined its effect as an induction agent clinically by assessing the hemodynamics and by using the BIS (Bispectral Index) where 20 of them were given ketofol, 20 were given propofol and the last 20 were given ketamine during

induction of anesthesia. During extubation; HR in the ketofol group (81.65 ± 2.60) was lower than in the propofol group (81.73± 3.93) but, with no statistical significance and MAP in the ketofol group (83.90± 3.30) was lower than in the propofol group (85.66± 3.43) with also, no statistical significance. This might be due to the lengthy procedure in their study and /or due to the small sample size of the groups. Our results came in agreement with Aboeldahab et al, as ketofol was associated with more stable hemodynamics than propofol during extubation. We attributed this to the good level of sedation of ketofol during suction and extubation due to the additive sedative effect of both ketamine and propofol.

We found that the effect of ketofol on HR was more important and more significant in stabilizing the hemodynamics than its effect on MAP when compared to popofol.

On the other hands, Jalili et al, who compared the effect of propofol and ketofol on the emergence delirium in 87 ASA I and II children aged from 3-12 years and underwent adenotonsillectomy, reported no statistically significant difference between the two groups regarding HR in the recovery room at 0, 10, and 20 minutes postoperatively. [19]

The smoothness of extubation without coughing, laryngospasm, and vomiting on the tube was examined in both groups and it was in favor of the KP group.

Recently, Aberra et al, in a study done on 120 pediatric patients aged from 2 to 15 years undergoing elective ophthalmic surgical procedures under general anesthesia using laryngeal mask airway (LMA) to compare the ketamine–propofol mixture (ketofol) with propofol only on the ease of laryngeal mask airway insertion conditions and hemodynamic effects during induction of general anesthesia, found that 54 patients in the ketofol group compared to 52 in the propofol group developed no cough, 6 patients in the ketofol group compared to 7 patients in the propofol group developed a slight cough (coughing which can occur immediately after LMA and subside by itself) and 1 patient in the propofol group developed gross cough (coughing which needs deepening of anesthesia to be relieved) with no significant difference between them. [17]

We also, reported that the sedation scores during suction and extubation were significantly lower in the KP group compared to the P group. We attributed this good level of sedation during suction and extubation to the analgesic effect of ketamine.

In our study, we reported that the KP group showed better airway response than the P group. One of the most adverse effects of the stress response on airway is cough. Kim and Bishop reported an incidence rate of 75% of cough in patients during emergence and extubation. [20] Hypertension, tachycardia, myocardial ischemia, and bronchospasm are adverse effects related to cough.

In our study, the majority of patients in the KP group [44 patients (83.1%)] developed better airway reflexes (grade 2,3) during suction better than the majority of patients in the P group [39 patients (73.6%)] developed higher degree of airway reflexes (grade 4 or 5). From all of the previous, we gave another explanation for the better hemodynamic stability during the extubation process in the KP group.

Aberra et al reported that no patient in the ketofol group developed laryngospasm while 2 patients in the propofol group developed partial laryngospasm with no statistical significance. They concluded that Ketofol provided equivalent laryngeal mask airway insertion conditions and it can be used as alternative propofol for LMA insertion. [17]

Patients in KP group showed higher level of sedation during the suctioning and extubation procedures when compared to those of the P group. This may be explained by the more sedative and more decreasing of the airway reflexes of ketofol during recovery in such short surgical procedures. As ketamine is a noncompetitive antagonist at N-methyl D-aspartate (NMDA) receptors and this blockade is dose-dependent. At low concentrations, analgesic properties are obvious, whereas at higher concentrations anesthetic properties become superior.[21] Rani et al showed a degree of sedation with dexmedetomidine 0.75 µg/kg during recovery compared to fentanyl 1 µg/kg when given 15 minutes before the end of the surgery .[18]

Ketofol, with decreased doses of both drugs, possesses the analgesic effects of ketamine and decreasing airway reflexes of propofol with hemodynamic stability i.e. it keeps the benefits of each drug and excluding the unwanted effects (analgesia of ketamine without increasing airway reflexes or sympathetic stimulation) and (Depressive effect of propofol on airway reflexes without hemodynamic instability) due to the additive effect of GABA agonism by propofol and (NMDA) antagonism by ketamine.[17] This may explain more hemodynamic stability, smoothness of extubation, decreased airway reflexes, and more sedative effect during suctioning and recovery in the KP group.

Conclusion

Giving ketofol during induction of general anesthesia in laparoscopic drilling of polycystic ovary provided a good sedation score during suction and extubation, better airway response during suction, smoothness of tracheal extubation and more stable hemodynamics than when propofol only was given.

Limitation and recommendations

We did this study in a relatively short surgical procedure that could be a limitation of our study. Also, limited follow-up time (20 minutes only). We recommend comparing the effect of both drugs on extubation and recovery from anesthesia in longer duration surgeries .

Abbreviations

ASA PS: Society of Anesthesiologists Physical Status.

BIS: Bispectral Index.

HR: Heart Rate.

GABA: Gama Amino Butyric Acid.

ICU: Intensive Care Unit.

LMA: Laryngeal Mask Airway.

MAP: Mean Arterial Pressure.

NIBP: Non-Invasive Blood Pressure.

NMDA: N-Methyl D-Aspartate

Declarations

- **Ethics approval and consent to participate:** Fayoum University Ethical Committee approval.
- **Availability of data and material:** All data are
- **Competing interests:** No competing interest.
- **Consent for Publication**: Not applicable.
- **Funding**: Fayoum University Hospital resources and own resources.

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- **Authors Contribution**: All authors contributed equally to this work. **AM** invited the idea, shared in the statistical analysis, and shared in writing the manuscript. **SG** shared in writing the manuscript and language editing. **JB** edited shared in writing, revised the manuscript, language editing and the corresponding author. All authors read and approved the manuscript.
- **Acknowledgments:** our families.

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Tables

Table 1

Observer assessment sedation score.

Observation	Score
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and\or repeatedly	3
Responds only after mild podding or shaking	2
Dose not responds to mild podding or shaking	1

Table 2

Grading of air way reflexes.

Grade	Description
1	Excellent (breathing well, no response to laryngoscopy& suctioning)
2	Good (breathing well, minimal grimacing response to laryngoscope& suctioning)
3	Satisfactory (breathing well coughing attempt to laryngoscopy& suctioning)
4	Poor (breathing well, coughing on tube laryngoscopy)
5	Very poor (breathing well, coughing on tube laryngoscopy)

Table 3

Smoothness of extubation.

Grade	Description
1	No coughing on endotracheal tube
2	Coughing on the tube
3	Vomiting
4	Laryngospasm

Table 4: Demographic data.

Parameters	Ketofol(KP) Group N=53 Mean±SD	Propofol (P) Group N=53 Mean±SD	*P*-Value
Age (years)	27.68± 3.67	26.49±3.06	0.073**
Height (cm)	164.13±5.20	166.25±5.05	0.036*, **
Weight (kg)	74.42±10.19	73.36±7.92	0.552**
BMI	27.70±4.18	26.56±2.80	0.103**
Surgical time (min)	23.5± 4.3	25.1±5.1	0.079**
Anesthesia time	31.4±5.4	33.2± 6.2	0.118**
Pethidine consumption N(%) **0** **25** **50**	 32 (60%) 18 (34%) 3 (6%)	 31 (95%) 13(25%) 9 (17%)	0.148#

* P-value is significant at or below 0.05. ** Using independent t test. # Using Chi-Square test.

Table 5: Hemodynamic variables at different study time points.

Group	Ketofol (KP) Group, N=53 Mean ± SD	Propofol(P) Group , N=53 Mean ± SD	*P*- value*	95% CI of the difference
MAP at (5) min before extubation.	107.19±10.34	115.64±11.01	<0.001**	-12.6, -3.4
MAP at the time of extubation.	107.49±12.52	112.96±11.10	0.019**	-10.0, -0.9
MAP at (5) min after extubation.	103.04±13.00	104.36±7.86	0.528	-5.4,2.8
MAP at (10) min after extubation.	94.92±5.59	97.66±4.61	0.007**	-4.7,-0.8
MAP at (15) min after extubation.	90.43±5.49	93.75±5.28	0.002**	-6.7, -1.8
MAP at (20) min after extubation.	83.30±5.99	90.15±3.86	<0.001**	-8.8, -4.9
HR/min at (5) min before extubation.	85.47±13.93	104.55±10.83	<0.001**	-23.8,-12.4
HR/min at the time of extubation.	87.75±1.22	103.72±6.48	<0.001**	-19.5,-12.4
HR/min at (5) min after extubation.	82.26±8.01	97.34±7.03	<0.001**	-118, -12.2
HR/min at (10) min after extubation.	79.25±7.36	92.81±7.00	<0.001**	-16.3,-10.8
HR/min at (15) min after extubation.	75.36±6.51	90.23±6.08	<0.001**	-17.3.-12.4
HR/min at (20) min after extubation.	72.98±5.40	86.38±5.07	<0.001**	-15.4,-11.4

* using independent t test, ** p-value is significant at or below 0.05.

Table 6: comparing outcome variables between the two groups.

			Ketofol (KP) group (N= 53)	Propofol (P) group (N= 53)	*P*-value for Chi Square test	Somers' D value (measure of trend)
Level of sedation during suction	1	N (%)	44 (83%)	10(18.9)	< 0.001*	0.675
	2	N (%)	7 (13.2%)	23(43.4)		
	3	N (%)	2 (3.8%)	20(37.7)		
Airway reflex	2	N (%)	11(20.8%)	2(3.8%)	< 0.001*	0.553
	3	N (%)	33(62.3%)	12(22.6%)		
	4	N (%)	5(9.4%)	33(62.3%)		
	5	N (%)	4(7.5%)	6(11.3%)		
Level of sedation at extubation	2	N (%)	7 (13.2%)	0	< 0.001*	1
	3	N (%)	46 (86.8%)	0		
	5	N (%)	0	53(100%)		
Smoothness of extubation	1	N (%)	53 (100%)	0	< 0.001*	1
	2	N (%)	0	20 (37.7%)		

	3	N (%)	0	30 (56.6%)		
	4	N (%)	0	3 (5.7%)		

* ***P***-value is significant at or below 0.05.

Figures

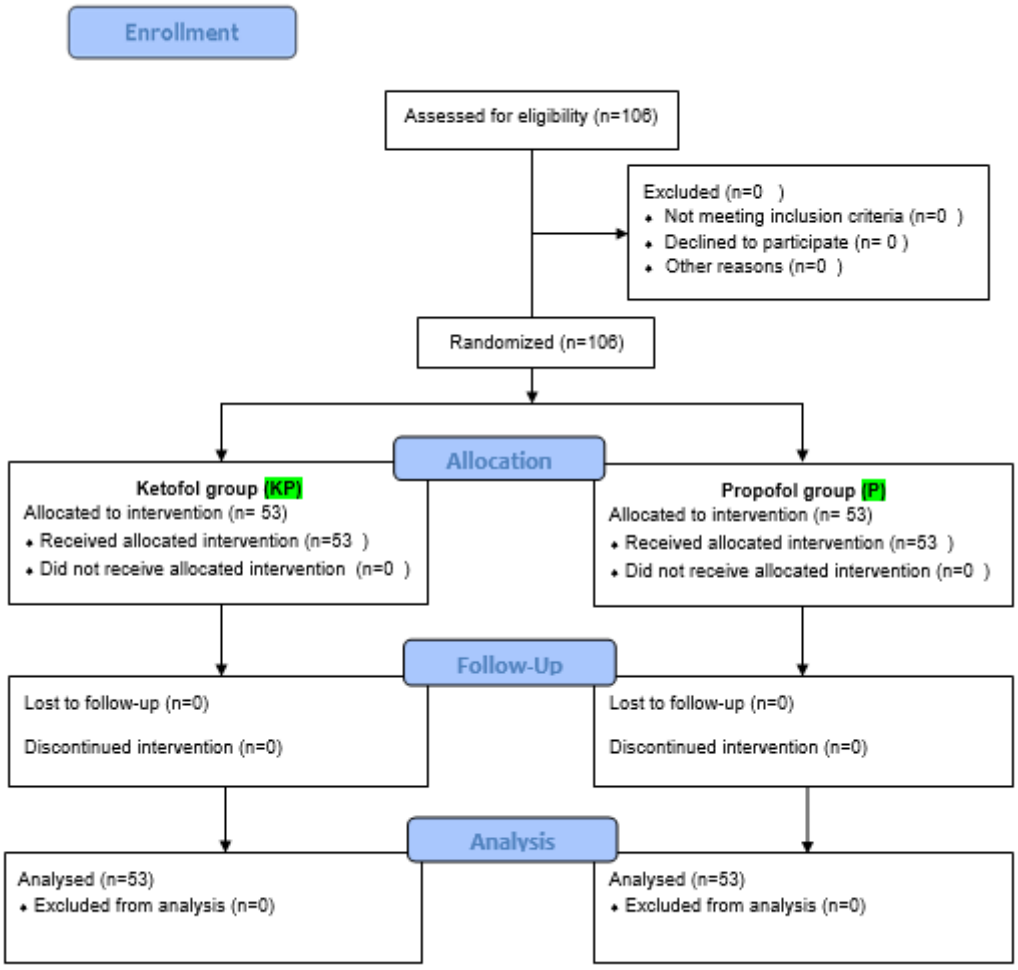

Figure 1

CONSORT flow diagram.

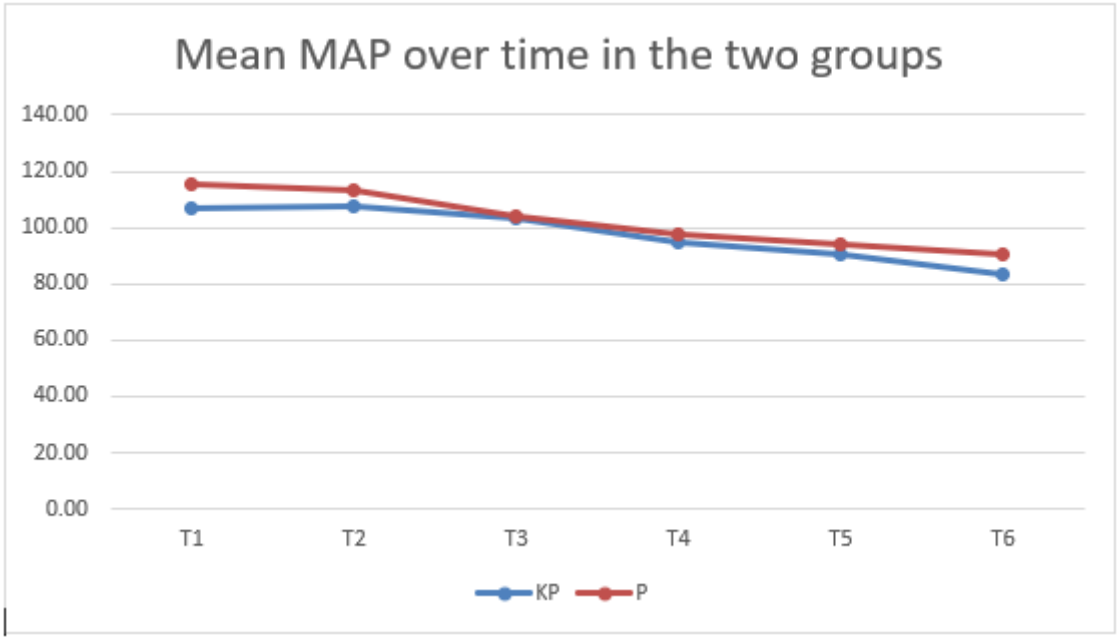

Figure 2

Mean arterial blood pressure (MAP) in the two groups at different study time points.

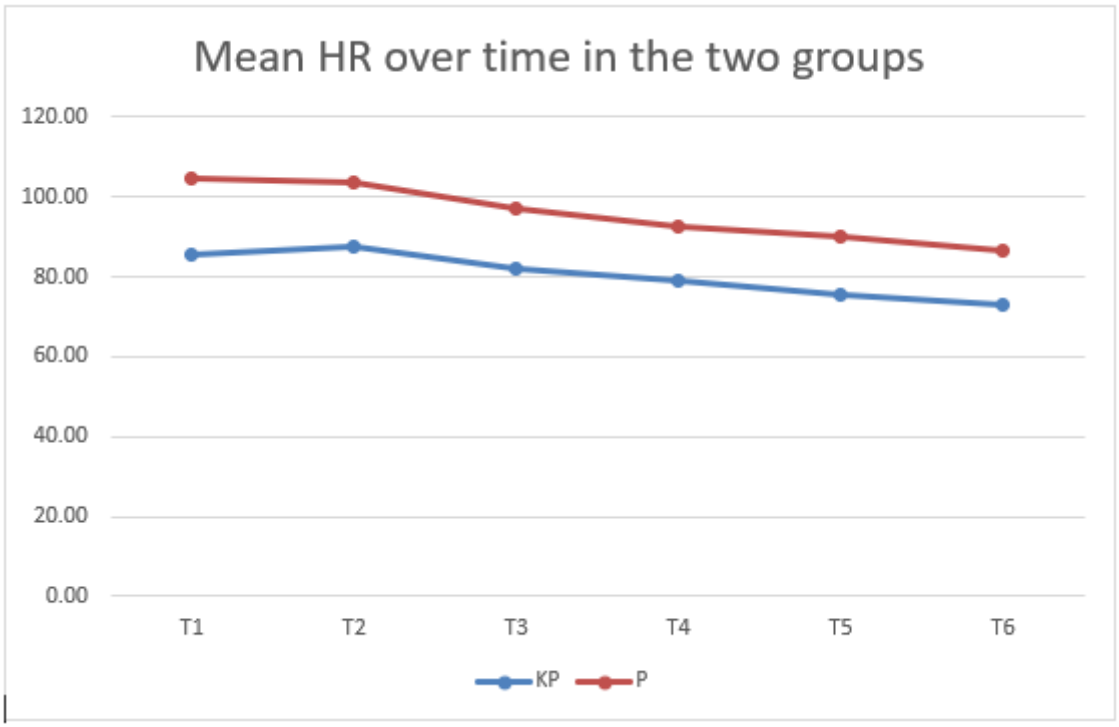

Figure 3

Mean Heart rate (HR) values in the two groups at different study time points.

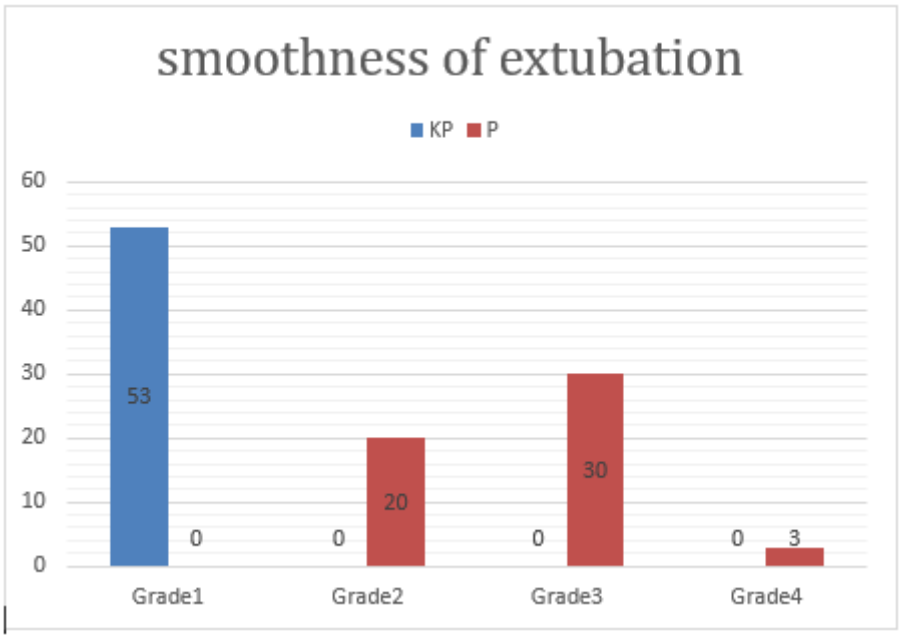

Figure 4

Smoothness of extubation in the two groups.

Supplementary Files

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- CONSORT2010Checklist12.doc