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COMPARATIVE STUDY BETWEEN KETOFOL VERSUS PROPOFOL ANESTHESIA FOR UTERINE CERVICAL DILATION AND CURRETTAGE

By

Abdelazim Abdelhalim Taha Hegazy

Department of Anesthesia and Intensive Care, Faculty of Medicine, Al-Azhar University, Egypt

ABSTRACT

Background: Ketofol (propofol-ketamine admixture) is used to compensate the hemodynamic chanages due to an induction of anesthesia. Uterine cervical dilation and curettage is a common procedure in day- care surgery.

Objective: Comparing the effectiveness of sub-dissociative dose of Ketamine ,in ketofol [group -I]on intraoperative hemodynamic stability, O_2%, pain ,anesthesia loading dose- verbal response time , incremental anesthesia ,last dose – verbal response time , surgeon's satisfaction and patient's satisfaction versus propofol alone [group-II].

Patients and method: Two hundred females, ASA I & II scheduled for uterine cervical dilation and curettage, were assigned to I or II groups. Intra-operatively the heart rate, non invasive blood pressure and O_2% were monitored and recorded at baseline time, 5^{th}, 10^{th}, 15^{th} and 20^{th} minutes. In recovery room, the pain was assesed by visual analogue scale and the patient's and surgeon's satisfactions were assesed and discharge criteria by Aldrete scoring system and post anesthesia discharge scoring system.

Results: The demographic characteristics, the duration of surgical procedure, and anesthesia loading dose - verbal response time showed no statistical difference, but incremental dose - verbal response time was significantly longer in group-I than group-II. Hemodynamic stability statistically had showed no significant differences. The ASS and PDSS were significantly higher in group-II than group-I at 5^{th} but insignificant and equal at 10^{th} minute. Pain was significantly lower in the group-I at 5^{th} and 10^{th} minutes than group-II.

Conclusion: The combination of propofol and sub-dissociate dose of Ketamine [Ketofol] was superior to Propofol alone and provided adequate sedation and analgesia for brief painful procedures.

Keywords: Uterine cervical dilation and curettage, Ketamine, Propofol, Ketofol, day care surgery.

INTRODUCTION

Day care gynecological procedures require the use of anesthetic agents which ensure rapid induction and recovery **(Hemani et al., 2015)**.Total intravenous anesthesia (TIVA) is a combination of hypnotic agents, analgesic drugs and may be muscle relaxants, excluding simultaneous administration of any inhaled drugs. Therefore, it can be an effective alternative to inhalational anesthesia and for ambulatory surgery when the speed and completeness of recovery are important. Drugs used for TIVA should have quick onset, smooth induction, easy maintenance, quick recovery and minimal side effects **(Babita et al., 2015).** Ideal drug for sedo-analgesia should have rapid onset and fast recovery time. However, there is still no consensus for best sedo-analgesic management for short-term procedures **(Hasan et al., 2013)**. Intra-

venous-based anesthesia techniques are widely used for the patient who must sleep during the procedure **(Uerpairojkit et al., 2003)**. Although propofol is the gold standard drug in day care procedures, it has its own side effects like apnea, cardio-vascular instability, pain on injection **(Hemani et al., 2015)**. Ketamine is an agent that provides sedation, analgesia and amnesia, and it might be an appropriate option for short-lasting procedures. However, it has cardio-vascular side effects and an induction of transitory psychotic episodes, together with delayed recovery and secretion increment **(Hasan et al., 2013).** Ketofol (propofol-ketamine admixture) is a combination of ketamine and propofol that is an agent of choice for various procedures **(Babita et al., 2015)**. The safety and efficacy of ketofol as a sedo-analgesic agent depend on the dose and the ratio of the admixture **(Daabiss et al., 2009)**. The ratios of 1:2, 1:3 and 1:4[sub-dissociative dose] ratios were very effective for the day case procedure **(Yanfen et al., 2012)**. Dilation and curettage (D C), a brief and painful procedure, is performed for the diagnosis and treatment of endometrial and intrauterine disorders. The procedure is one of the most frequently performed gynecological surgical procedures. It causes considerable pain during cervical dilation and tissue extraction **(Yuce et al., 2013).**

The present study aimed to compare the effectiveness of sub-dissociative dose of ketamine - propofol admixture on intraoperative hemodynamic stability, O_2%, pain, anesthesia loading dose-verbal response time, incremental anesthesia last dose – verbal response time, surgeon`s satisfaction and patient`s satisfaction versus propofol alone group.

PATIENTS AND METHODS

The study was designed as a prospective randomized double blind study, and was conducted at Al-Azhar University's Hospitals over a period of twelve months from the beginning of December 2014 to the end of November 2015. Two hundred patients, according to the American Society of Anesthesiologist Physical Status Classification (ASA) I or II in bearing period of age (22-50 years old), were scheduled for uterine cervical dilation and currettage [D&C] procedure. The study was done after obtaining the research / ethics committee approval of Al-Azhar University, and patient's written informed consents. The patients - according to computer generated randomization with sealed envelope technique - were assigned to ketamine – propofol admixture [group-I] or propofol [group-II]. Exclusion criteria were ASA ≥ III, BMI ≥35 Kg / M^2, history of allergic reaction to the drugs of study, chronic use of sedatives, opioid analgesics and presence of a psychiatric disorder with chronic medical treatment, presence of liver or kidney dysfunctions, cardiac and endocrine diseases.

Preparation of drugs; For group-I,1 ml of 50 mg/ml ketamine was added to 20 ml of propofol 10 % in 20 ml syringe to make a ketofol admixture as 1:4 ratio . For group-II, propofol 10% was made in 20 ml syringe.

Anesthetic Technique: Anesthesia was achieved by total intravenous anesthesia (TIVA) technique and O_2 face- mask via Drager Fabius GS anesthesia machine for

all patients, the patients were pre-oxygenated with 100% oxygen for 5 minutes. The patients in both groups had received 0.5 ?g / kg^{-1} fentanyl before induction. Lignocaine 1mg / kg^{-1} was given intravenously just before anesthetic agents in both groups. Propofol or ketofol was given as 1.5-2 mg / kg^{-1} slowly until the patient has no longer responded to her name being called loudly and loss of the eyelash reflex.

The additional 5ml of prepared drugs were given when the patient became light as evidenced by change in heart rate, lacrimation or limb movements. The heart rate, systolic arterial blood pressure, diastolic arterial blood pressure, and oxygen saturation were monitored and recorded at baseline time (at an induction of anesthesia), 5^{th} , 10^{th} , 15^{th} ,20^{th} minutes after an induction of anesthesia and repeated every five minutes until the end of operation. The operation details regarding the duration of surgical procedure, anesthesia loading dose - verbal response time (the patients were able to recall their name and date of their birth), and the incremental anesthesia last dose (last injected dose) - verbal response time were recorded. Adverse events such as apnea, any patient`s abnormal sounds, muscle movements and airway problems inform of laryngeal spasm were recorded during operation and in recovery room. Intravenous fluid (4 ml /kg) of normal saline or Ringer`s lactate solutions were used as a routine peri-operative and intra-operative fluid therapy. Midazolam (0.05 mg/kg^{-1}) IV was given as pre-medication.

In recovery room, patient's clinical status were assessed according to the Aldrete Scoring system (ASS) **(Aldrete, 1995)**, and discharge criteria was assessed according to Post Anesthetic Discharge Scoring System (PADSS) **(Heather and Bscn, 2006)**. A Visual Analog Scale (VAS) was used to evaluate pain intensity (**Warden et al., 2003**). All patients were assesed at 5^{th} and 10^{th} minutes post-operativly.

Intramuscular voltaren (75 mg) was planned as a rescue analgesic agent if the patients need in recovery time.

Patient's and surgeon's satisfaction were rated on a scale of 1 to 4 (1=perfect, 2=good, 3=moderate, 4=bad) **(Arikan et al., 2015)**. The surgeon's satisfaction was assessed after completion of the operation. Patients were visited 2 hours later on the floor to assess their satisfaction.

Statistical analysis: Data were checked, entered and analyzed using SPSS software statistical computer package 22 data using student's t-test and mean ± SD, numbers and percentages when appropriate. $P < 0.05$ was considered statistically significant.

RESULTS

Two hundred patients successfully had completed this study. The demographic characteristics including age, weight, height and BMI of two groups, there were no statistically differences between two groups (Table 1).

Table (1): Patient's demographic data (mean ± SD)**.**

Groups / Parameters	Group-I (n = 100)	Group-II (n =100)	P-value
Age (years)	30.65 ± 8.190	31.70 ± 8.646	0.352
Weight (Kg)	72.9 ± 10.12	73.17 ± 9.8	0.848
Height (cm)	170 ± 10.93	169 ± 10.31	0.506
BMI (Kg / M^2)	24.65 ± 3.34	25.41± 3.48	0.121

Group-I: ketofol admixture, group-II: propofol alone.

There were no differences between two groups in the duration of surgical procedure and anesthesia loading dose - verbal response time, but it had showed highly significant difference in the last incremental dose - verbal response time. Patients awaked early in group-II than in group-I group but recovery's staying time was same in both groups (Table 2).

Table (2): Operation details (mean ± SD).

Groups / Parameters	Group-I (n = 100)	Group-II (n =100)	P-value
Duration of operation (starting – shifting to recovery room) [minutes].	19.25 ± 4.94	19.2 ± 3.36	0.933
Loading – verbal response time [minutes].	27.85 ± 3.65	26.95 ± 2.98	0.244
Last incremental dose - verbal response time [minutes].	9.7 ± 2.90	7.1 ± 0.85	0.001

Group-I: ketofol admixture, group-II: propofol alone

Regarding the hemodynamic stability, there were no statistically significant differences in heart rate, systolic and diastolic blood pressure at baseline, 5^{th}, 10^{th}, 15^{th} and 20^{th} minute values among two groups, for all comparison readings (table 3).

Table (3): Hemodynamic changes (mean ± SD).

Parameters / Groups	Time of measurement	Group-I (n-100)	Group-II (n-100)	P-value
Heart Rate	At base line	104 ± 5.7	105 ± 4.8	0.181
	At 5th minute	102 ± 3.2	101.5 ± 3.1	0.263
	At 10th minute	100 ± 4.8	99 ± 4.1	0.114
	At 15th minute	98.5 ± 3.2	99 ± 3.1	0.379
	At 20th minute	94 ± 6.2	93.5 ± 5.2	0.537
Systolic arterial blood Pressure	At base line	123 ± 5.3	124 ± 5.2	0.179
	At 5th minute	122 ± 4.7	121 ± 4.1	0.110
	At 10th minute	118 ± 6.1	119 ± 6.8	0.275
	At 15th minute	121 ± 5.2	120 ± 4.9	0.163
	At 20th minute	124 ± 3.2	125 ± 3.6	0.039
Diastolic arterial blood pressure	At base line	73 ± 7.2	74 ± 8.9	0.383
	At 5th minute	72.3 ± 3.2	73 ± 3.0	0.112
	At 10th minute	68 ± 5.2	69 ± 4.8	0.159
	At 15th minute	71 ± 2.5	70.5 ± 2.1	0.127
	At 20th minute	75.5 ± 2.1	76 ± 2.4	0.118

Group-I: ketofol admixture, group-II: propofol alone

In recovery, the Aldrete Scoring System (ASS) and Post Anesthetic Discharge Scoring System (PADSS) were same, but significantly higher in group-II than group-I at 5th minute in both groups. Regarding pain intensity, Visual Analogue Score was significantly lower in group-I with no pain, and no Rescue painkiller needed at 5th and 10th minutes than group-II (Table 4).

Table (4): Recovery details (range).

Parameters / Groups	Group-I (n = 100)	Group-II (n =100)	P-value
ASS and PADSS. at 5th minute	9.10 (8-10)	9.95 (8-10)	0.01
ASS and PADSS. at 10th minute	10(9-10)	10 (9-10)	1.00
VAS at 5th minute	0(0-0)	4 (3-5)	>0.001
VAS at 10th minute	0(0-0)	3 (2-4)	>0.001
Surgeon`s satisfaction	2(2-2)	2(2-2)	---
patient's satisfaction	1(1-1)	1(1-1)	----

Aldrete Scoring System (ASS), Post Anesthetic Discharge Scoring System (PADSS) and Visual Analogue Scale (VAS), Group-I: ketofol admixture, group-II: propofol alone.

Regarding surgeon's satisfaction and patients' satisfaction scores were similar in two groups**.** (Table4**).** Regarding adverse effects in intra-operative and in Recovery room were insignificant differences between both groups except the patient's abnormal sounds intra-operative were significant (Table 5).

Table (5): Adverse events in intra-operative and in Recovery Room (%).

Groups / Parameters	Group-I (n=100)	Group-II (n= 100)	P-value
Airway problems inform of laryngeal spasm	0(0 %)	0(0 %)	----
Muscle movements	0(0 %)	0(0 %)	----
Apnea	0(0 %)	0(0 %)	----
Patient`s abnormal sounds intra-operatively.	0(0 %)	30 patients (31.6 %)	0.001

Group-I: ketofol admixture, group-II: propofol alone

DISCUSSION

The combination of propofol and ketamine provides an adequate sedation and analgesia for brief painful procedures **(Willman & Andolfatto, 2007 and Tosun et al., 2008).** There are limited numbers of investigation concerning the use of propofol-ketamine for sedation in gynecological procedures **(Sahin et al., 2012)**. The present study showed that no statistically difference between two groups in the duration of surgical procedure and anesthesia loading dose - verbal response time, but it had showed highly significant difference in the last incremental dose - verbal response time (patients awaked early in group-II than in group-I). **Aouad et al. (2008**) reported that ketamine has analgesic effects in sub-dissociative doses, and when used in combination with propofol. It had been shown to reduce propofol expenditure and protect hemodynamic stability. Regarding hemodynamic stability, there was no significant difference between the two groups. This was in line with the study of **Hasan et al. (2013**) who showed that both groups had similar hemodynamic effects, and **Somchai (2014**) who mentioned that the combination of propofol and ketamine has several benefits because of hemodynamic stability.

Patients in group-II had shorter recovery time at 5^{th} minute than that group-I, but the patients had the same recovery time at 10^{th} minute in both groups, and same recovery's staying time. **Akin et al. (2005)** compared a combination of propofol and fentanyl with propofol and ketamine and observed that there was no difference in the recovery times. **Sahin et al. (2012)** compared alfentanil (10 ?g / kg^{-1}) and ketamine (0.5 mg/kg) in combination with propofol (0.7 mg/kg^{-1}) for DC procedures, and found the orientation time was longer in ketamine group than in the alfentanil group.

Patients in group-II had rescue painkiller medications. However ketofol had provided comfortable analgesia and no need additional doses of rescuer

painkiller medications in recovery. The present study had shown that the time to reach Aldrete score or post anesthesia discharge score of 10 degree was earlier in the group-II than group-I at 5th minute, but the discharge time was same in the both groups.

Surgeon's satisfaction and patients' satisfaction scores were similar in the two groups **Babita et al. (2015)** showed that the satisfaction scores for both patients and gynecologists were similar.

CONCLUSION

The combination of Propofol and Ketamine [Ketofol] was superior to Propofol alone, and provide adequate sedation, analgesia and satisfaction for brief painful procedures. Ketamine as an adjuvant to propofol improved the quality of the anesthetic technique with minimal side effect.

REFERENCES

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

2. **Aldrete J A. (1995):** The post anesthesia recovery score visited. J. Clin. Anaesth., 7: 89-91.

3. Aouad T, Moussa R and Dagher M. (2008): Addition of ketamine to propofol for initiation of procedural anesthesia in children reduces propofol consumption and preserves hemo-dynamic stability. Acta Anaesthesiol Scand., 52: 561-565.

4. **Arikan M, Aslan B, Arikan O and Horasanli E. (2015):** Comparison of propofol-remifen-tanil and propofol-ketamine combination for dilatation and currettage: a randomized double blind prospective trial. European Review for Medical and Pharmacological Sciences, 19: 3522-3527.

5. **Babita R, Dinesh K, Sangita R and Gurdeep S. (2015):** A Comparative Evaluation of Propofol-Ketamine and Propofol- Fentanyl as T.I.V.A Techniques In Terms Of Haemodynamic Variables and Recovery Characteristics in Minor Surgeries. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), 14 (4): 19-26.

6. **Daabiss M, Medhat E and Rashed A. (2009):** Assesment of different concentration of ketofol in procedural operation .British Journal of Medical Practionars, 2(1)27-31.

7. **Hasan Y, Ahmet K, Nuray A, Tekin B, Mahmut A K, Evren B, Inanc H, Aysun C, Adnan I, Nese G and Saban Y. (2013):** Propofol-Ketamine Combination has Favorable Impact on Orientation Times and Pain Scores Compared to Propofol in Dilatation and Curettage. Acta Medica, Mediterranean, 29: 539-44.

8. **Heather E and Bscn N. (2006):** From Aldrete to PADSS: Reviewing Discharge Criteria after Ambulatory Surgery. Journal of Peri Anesthesia Nursing, 21(4):259-267.

9. **Hemani A, Valsamma A, John A, and Dootika L. (2015):** Ideal anesthetic agents for daycare gynecological procedures: A clinical trial comparing thiopentone with ketamine as adjuncts to propofol. Advanced Biomedical Research, 4: 81-87.

10. **Sahin L, Sahin M, Aktas O, Kilic E and Mandoll E. (2012):** Comparison of propofol/ketamine versus propofol / alfentanil for dilatation and curettage. Clin Exp Obstet Gynecol., 39: 72-75.

11. **Somchai A. (2014):** Ketofol: A Combination of Ketamine and Propofol. J Anesth Crit. Care Open Access 1, (5): 00031-33.

12. **Tosun Z, Esmaoglu A and Coruh A. (2008):** Propofol-ketamine vs. propofol-fentanyl combinations for deep sedation and analgesia in pediatric patients undergoing burn dressing changes. Pediat. Anesth. , 18: 43-47.

13. **Uerpairojkit K, Urusopone P and Somboonviboon W. (2003):** A randomized controlled study of three targets of propofol plasma concentration in patients undergoing

uterine dilation and curettage. J. Obstet Gynaecol Res., 29: 79-83.

14. **Warden V, Hurley C and Volicer L. (2003):** Development and psychometric evaluation of the pain assessment in advanced dementia (PAINAD) scale. Journal of the American Medical Directors Association, 4:9-15.

15. **Willman V and Andolfatto G. (2007):** A prospective evaluation of ‘‘Ketofol’’ (ketamine/propofol combination) for procedural sedation and analgesia in the emergency department. Ann Emerg Med., 49: 23-30.

16. **Yanfen W, Yanhua F, Sujan S P, Changji Y and Haichun M. (2012):** A randomized double-blind controlled study of the efficacy of ketofol with propofol-fentanyl and propofol alone in termination of pregnancy, African Journal of Pharmacy and Pharmacology, 6(34):10-14.

17. **Yuce H, Kucuk A, Altay N, Bilgic T, Karahan A, Buyukfirat E, Havlioglu I, Yalcin S, Camuzcuoglu A, Incebiyik A and Hilali G. (2013):** Propofol-ketamine combination has favorable impact on orientation times and pain scores campared to propofol in dilatation and curettage. A randomized trial. Acta Medical Mediterranean, 29: 539-544.

دِراسةٌ مقَارنةٌ بين إستخدام عِقار البروبوفول منفردا و عِقار الكيتوفول (خلّطة من عقارى البروبوفول والكيتامين) للتخدير أثناء عملية توسيع عنق وكحت الرحم

عبد العظيم عبد الحليم طه حجازي

قسم التخدير والعناية المركزة - كلية الطب- جامعة الأزهر

خَلّفِيَةُ الْبَحْثُ : عَمَلِيَاتُ تُوسِيع عُنْق الْرَحِم وَكَحْتِهْ وتَنظيفه بقسمِ العملياتِ الخاصة بحالات النساء والولادة التى يطلق عليها عمليات اليوم الواحد ، ويستخدم فيها عقار الكيتوفول وهو خليط من البروبوفول و الكيتامين لتُّغلب على الهبوط بالدورة الدموية اثناء عملية التخدير .

الهدفُ من هذه الدراسةِ: تقييمِ ومقارنة تأثير جرعة الكيتامين المضافة لعقار البروبوفول(الكيتوفول) على استقرار الدورة الدموية ونسبة الأكسجين بالدم ، الشعور بالألم ، زمن وقت العملية من بداية حقن الجرعة الاولى الى وقت إفاقة المريض بغرفة الافاقة ، الوقت من اخر جرعة إضافية أثناء العملية الى وقت الإفاقة ايضا بغرفة الافاقة ، تسجيل حدوث تشنجات بالحنجرة أثناء عملية التوسيع لعنق الرحم وأخيرا تقيس درجة الوعى ومدى الحاجة الى مسكن إضافى بغرفة الإفاقة بين مريضات المجموعتين كما تقيس درجة رضى كلا من الجراح والمريض عن كفاءة وفاعلية عملية التخدير بعقار الكيتوفول.

المرضى وطريقةُ البحث :أُجريت الدراسة على مائتين من المريضات وكن من الدرجة الأولى والثانية البدنية على مقياس جمعية التخدير الامريكية، وتم توزيعهن على مجموعتين عشوائيا بطريقة الكمبيوتر والخطاب ألمغلق: المجموعة الأولى مجموعة البروبوفول والثانية الكيتوفول. وقد تم تسجيل نبض القلب والضغط الانقباضى والانبساضى و نسبة تشبع الدم بالأكسجين قبل التخدير مباشرة ،وبعد خمس، وعشر، وخمسة عشر وعشرين دقيقة وكذلك ملاحظة حدوث تشنجات بالقصبة الهوائية .كما تم حساب الوقت من بداية إعطاء عِقار التخدير، الى وقت الافاقة الكاملة ونفس الشئ بالنسبة لآخر جرعة إضافية حتى وقت الافاقة الكاملة قد تم مقارنة سرعة الوصول الى درجة الوعى الكامل والشعور بالألم من عدمه والحاجة إلى مسكن إضافى، وكذلك مدى رضى المرضى والجراحين عن فاعلية وكفاءة عملية التخدير .

النتائج: البيانات الفردية ، وقت العملية وكذلك وقت زمن العملية من وقت الجرعة الأولى حتى درجة الوعى الكامل بالتنبيه لا تظهر فروقات ذات معنى بين المجموعتين وقد أثبتَ التحاليل وجود فروقات ذات معنى كبير فى بعض المقارنات حيث كان الوقت طويل بين الجرعة الاخيرة ووقت الافاقة فى مجموعة الكيتوفول وقصيرة بمجموعة البروبوفول، واثبت وجود تشنجات حنجرية اثناء العملية فى مجموعة البروبوفول. كما ثبت من التحليل الاحصائى للدورة الدموية من النبض والضغط (الانقباضى و الانبساطى) ونسبة تشبع الدم بالأكسجين عدم وجود فروقات ذات معنى بين المجموعتين .كماأثبتت التحليل الإحصائية وجود فرق فى درجة الوعى بين المجموعتين حيث كانت اسرع فى مجموعة البروبوفول عند الدقيقة الخامسة، ولكن لا فرق عند الدقيقة العاشرة ولا فى وقت الاقامة بغرفة الافاقة ، كما ثَبَتَ الفرق الواضح فى عدم حاجة مريضات مجموعة الكيتوفول لأى مسكنات فى غرفة الافاقة و لا أخذ أي منهن لمسكن إضافى.

الاستنتاج :خليط عقاري البروبوفول والكيتامين يحدث درجة عالية من التخدير وعدم الشعور بالألم فى عمليات اليوم الواحد.