Original Article

Ideal anesthetic agents for day-care gynecological procedures: A clinical trial comparing thiopentone with ketamine as adjuncts to propofol

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Abstract

Background: Day-care gynecological procedures require the use of anesthetic agents, which ensure rapid induction and recovery. Although propofol is the gold standard drug in day-care procedures, it has its own side effects like apnea, cardiovascular instability, pain on injection, as well as its cost. The ideal drug combination to achieve this end remains elusive. Therefore, a combination of propofol, thiopentone, and ketamine may be a better alternative.

Materials and Methods: This prospective, double-blind, randomized study was conducted on 60 women, aged 18-50 years, American Society of Anesthesiologists (ASA) physical status 1 and 2, undergoing day-care gynecological surgeries. The patients were allocated to two groups. Group T received an admixture containing 10 ml of 1% propofol and 10 ml of 1.25% thiopentone. Group K received an admixture containing 10 ml of 1% propofol and 10 ml of 0.5% ketamine.

Results: There was less variation in the mean systolic blood pressure of patients in Group K as compared to patients in Group T. The mean total dose of propofol required in Group K (0.85 mg/kg) was significantly less than that required in Group T (1.12 mg/kg) ($P = 0.0004$). The mean recovery time in Group T (3.67 minutes) was significantly less than in Group K (6.27 minutes; $P = 0.0001$). However, the mean discharge time in both the groups was similar. ($P = 0.7392$). The results were analyzed statistically using the Student's *t*-test and the Fisher's exact test.

Conclusions: Both the propofol-thiopentone and propofol-ketamine admixtures provided adequate anesthesia. Propofol-ketamine proved superior to propofol-thiopentone in terms of hemodynamic stability and requirement of a lesser total dose of propofol. However, the patients in the propofol-thiopentone group had faster recovery.

Key Words: Day care, gynecological surgeries, ketamine, propofol, thiopentone

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INTRODUCTION

An ideal intravenous anesthetic regimen used in day-care surgery should provide rapid recovery and early discharge with minimal side effects, at a reasonable cost. Propofol has emerged as the gold standard in day-care surgery. Thiopentone and ketamine are time tested agents, but with disadvantages like prolonged recovery,

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emergence delirium, and postoperative nausea and vomiting. Therefore, a combination of propofol with either thiopentone or ketamine may be a better alternative. Naguib *et al*.[1] has also showed hypnotic synergism between thiopentone and propofol. A combination of propofol-ketamine offered advantages both in the efficacy and tolerability, as compared to propofol-fentanyl.[2] When the combination of propofol-ketamine was compared with propofol-thiopentone, propofol-ketamine was found to be better, because it had greater hemodynamic stability and superior airway maintenance.[3]

This prospective, randomized, double-blind study comparing propofol-ketamine and propofol-thiopentone was conducted in the Department of Anesthesiology, as very few studies have explored the use of these mixtures for day-care gynecological procedures.

MATERIALS AND METHODS

After approval from the Institutional Ethics Committee and Review Board and after obtaining written informed consent, this double-blind, randomized study was conducted on 60 adult patients, who were aged 18-50 years, of ASA 1 or 2, weighing 50-70 kg, undergoing minor gynecological surgeries. Patients who had hypotension, history of ischemic heart disease, egg allergies, or intake of psychotropic or opioid medication in the preceding 48 hours were excluded from the study. The relevant investigations were done after taking a detailed history and patients were kept nil orally for six hours before surgery. All the patients were given injection midazolam 0.03 mg/kg and injection paracetamol 1 g intravenously (IV) ten minutes (min) before induction.

The groups were allocated using a permuted randomized block design, in blocks of four. Each envelope had four slips, one slip was picked and the drug was freshly prepared by an anesthetist who was not involved in the study. These slips were numbered 1-60 in such a manner that thirty patients received propofol-thiopentone (Group T) and thirty patients received propofol-ketamine (Group K). Group T received an admixture containing 10 ml of 1% propofol and 10 ml of 1.25% thiopentone and Group K received an admixture containing 10 ml of 1% propofol and 10 ml of 0.5% ketamine.[3] The drug admixture was injected intravenously at a rate of 4 ml/10 seconds until there was loss of consciousness. The same drug mixture prepared in each group was used initially as bolus drug and later for supplemental drug dosages. All patients were maintained on spontaneous ventilation using the Mapleson A circuit and supplemental doses of 2 ml of the study drug were given, as required, during the intraoperative period.

The preinduction and intraoperative heart rate, blood pressure, and oxygen saturation values were recorded at 1, 5, and 10-minute intervals, and thereafter, every five minutes till the end of the procedure.

Side effects such as pain on injection (patients were told to inform if they experienced pain at the injection site, when an initial dose of 1 or 2 ml of the drug mixture was being injected), hemodynamic instability, apneic episodes, salivation, presence of laryngospasm or bronchospasm, as well as any occurrence of nausea or vomiting were noted. Apnea was defined as the loss of spontaneous respiratory effort for 20 seconds or more, along with oxygen desaturation to less than 90%. Whenever there was apnea patients were manually ventilated till spontaneous respiration resumed.

The recovery time was calculated from the discontinuation of the study drug till the patients started following verbal commands. Discharge time from the recovery was noted. Patients were discharged according to the Post Anesthesia Discharge Scoring System, when the score was more than 9.

The sample size was calculated as 29 on each arm, with a total of 58; using Stat Calculator on Epi Info (version 8), assuming the difference between the means of the top-up dose to be 3.5 ml, a power of 80%, and α of 95%. To account for any dropouts from the study we took the sample size as 60. The results were analyzed statistically using the Student's *t*-tests and Fisher's exact test. A *P*-value of < 0.05 was regarded as statistically significant.

RESULTS

Seventy patients were screened for the study, of which sixty fulfilled the inclusion criteria [Figure 1]. Patients in both the groups were comparable with respect to age, weight, duration of surgery, baseline heart rate, and systolic and diastolic blood pressures [Table 1].

Table 1: Patient characteristics

Parameter	Group T (%)	Group K (%)	*P*-value
Age (years)	34.47±8.38	33.63±9.27	0.7128
Weight (kg)	57.37±6.96	58.20±7.83	0.6638
Duration of surgery (minutes)	20.50±6.07	20.83±6.58	0.8402
Type of surgery n (%)			
Suction and evacuation	9 (30)	7 (23)	
Dilatation and curettage	10 (33)	16 (54)	
Fractional curettage	11 (37)	7 (23)	
Baseline hemodynamic parameters			
Heart rate (beats/minute)	91.73±14.69	88.00±12.52	0.2968
SBP (mm Hg)	124.63±12.80	121.40±11.90	0.3144
DBP (mm Hg)	79.63±6.70	78.67±7.83	0.6140

SBP: Systolic blood pressure, DBP: Diastolic blood pressure

On analysis of the intraoperative hemodynamic variables, Group T had a statistically significant decrease in systolic blood pressure as compared to the preinduction value at all the time intervals studied. In Group K, a significant decrease in systolic blood pressure occurred only at one minute and five minutes after induction. There was a significant decrease in diastolic blood pressure at one minute-, five minute-, and ten minute-intervals, as compared to the baseline value in Group T. However, there was no significant change in Group K [Figure 2].

In Group T, the heart rates were stable at all time intervals studied, while in Group K, there was a significant increase in heart rate from the preinduction value at one minute and five minutes [Figure 3]. The oxygen saturation of patients during anesthesia was comparable between the two groups.

The mean induction drug volumes of the admixtures were comparable in both the groups (P = 0.839). However, the mean supplemental drug volume required was significantly greater in Group T than in Group K (P = 0.001). Patients in Group K required a significantly lesser total mean dose of propofol as compared to patients in Group T (P = 0.0004) [Table 2].

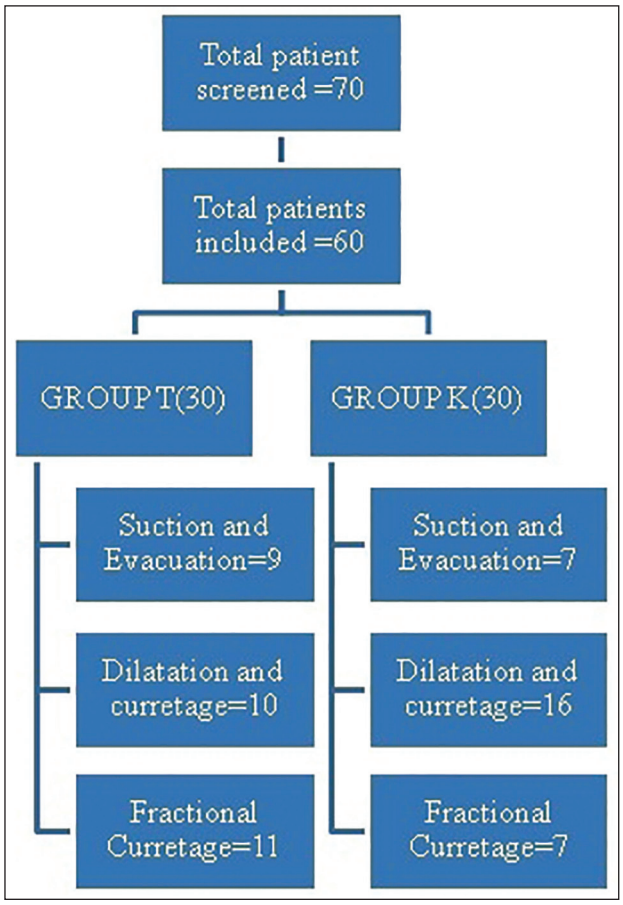

Figure 1: Flow diagram of the type of surgeries

Patients in Group T had a shorter mean recovery time than those in Group K (P = 0.001); however, the discharge times in both groups were comparable (P = 0.7392) [Table 3].

Very few side effects were observed in both groups. Apneic episodes occurred in two patients in Group T, while one patient in Group K had an episode of emergence delirium. These were nonsignificant differences.

DISCUSSION

Minor gynecological procedures are usually performed on a day-care basis. Day-care anesthesia requires anesthetic agents with a rapid onset, adequate depth, rapid recovery, minimal side effects, and with a lower cost. Various induction agents such as thiopentone, propofol, midazolam, fentanyl, and ketamine have all been used for this purpose, each having its own side effects. However, thiopentone, ketamine, and propofol have acquired a unique role in clinical practice.

Several studies[3,4] have demonstrated a synergistic interaction between thiopentone and propofol, as they have similar binding sites on the GABA receptor A prospective study[5] done on 180 female patients, who presented for minor gynecological surgeries has reported that the mixture of propofol and ketamine is additive at the hypnotic and anesthetic end points.

Table 2: Drug dosages used

Parameter	Group T	Group K	*P*-value
Bolus drug volume (ml)	7.73±2.21	7.87±2.35	0.8126
Supplemental drug volume (ml)	17.47±5.41	11.93±3.98	0.0001*
Total propofol dose (mg/kg)	1.12±0.32	0.85±0.20	0.0004*

*P-value < 0.05

Table 3: Recovery characteristics

Parameter	Group T	Group K	*p*-value
Recovery time (minutes)	3.67±1.09	6.27±2.02	0.0001*
Discharge time (hours)	5.93±0.37	5.87±0.90	0.7392

*P-value < 0.05

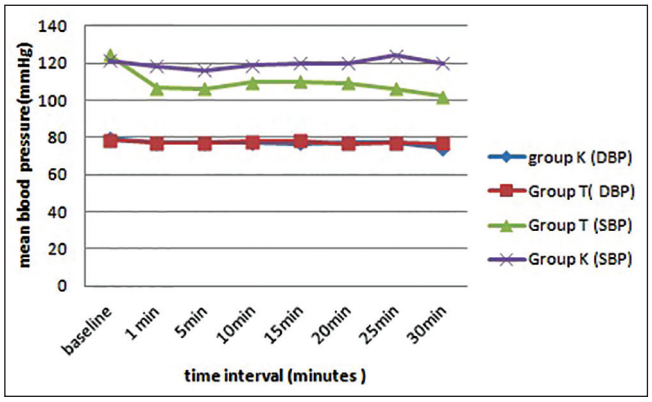

Figure 2: Comparison of mean blood pressures between two groups

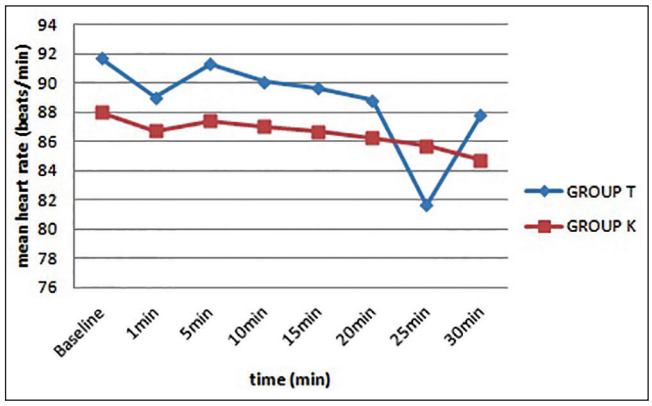

Figure 3: Comparison of heart rates between two groups

Therefore, we proposed to compare the admixtures of propofol-thiopentone and propofol-ketamine in terms of their hemodynamic stability, side effects, dosage required, and recovery profiles.

Our patients were predominantly young women posted for procedures like dilatation and curettage and fractional curettage and comparable with respect to their demographic characteristics.

The patients in Group T had a significantly greater decrease in systolic blood pressure as compared to Group K at various time intervals. This can be explained by the fact that propofol decreases myocardial contractility and peripheral vascular resistance thus decreasing systolic as well as diastolic blood pressures. Thiopentone too decreases myocardial contractility and peripheral vascular resistance, thus decreasing systolic blood pressure as well as diastolic blood pressure. Ketamine is a myocardial stimulant and increases peripheral vascular resistance, thus increasing systolic and diastolic blood pressures. Hence, with a mixture of propofol-ketamine the decrease in blood pressure caused by propofol is compensated, by the increase caused by ketamine.[3,5-8]

The mean heart rate between the two groups did not differ significantly. This can be explained by the fact that propofol, due to its central vagal activity causes bradycardia.[9] Ketamine due to its myocardial stimulation actively causes tachycardia.[10] Thiopentone too causes tachycardia.[11] Therefore, mixing propofol with ketamine and thiopentone compensates for the decrease in heart rate caused by propofol.[3]

Even as the induction drug volumes have not varied significantly between the two groups, the supplemental volumes required to maintain anesthesia were significantly higher in Group T as compared to Group K. Similar results have also been reported in patients undergoing minor gynecological procedures, by Vora *et al.*, in 2005.[3] This is probably because of the excellent analgesic properties of ketamine. The total dose of propofol required in our study in Group K was 0.85 mg / kg ± 0.20, which was significantly less than that in Group T (1.12 mg/kg ± 0.32). This may also be explained by the fact that Group K contained the potent analgesic ketamine.

In our study, two patients receiving propofol-thiopentone developed apnea. We observed loss of respiratory efforts after a bolus dose of the admixture, which lasted for 30 and 40 seconds, respectively, but when the patients were ventilated with a face mask, they regained spontaneous respiration and the saturation picked up, so there was no change in oxygen saturation between the two groups. Patrick *et al.*,[12] reported reduction in tidal volume as well as in respiratory rate with the use of thiopentone for induction of anesthesia. Goodman *et al.*,[13] while studying the respiratory effects of propofol in healthy premedicated patients, reported that there was a decrease in respiratory rate and a slight increase in tidal volume. Ketamine generally preserved airway patency and respiratory function. Hui *et al.*,[5] showed that ketamine had no influence on the incidence of apnea after propofol administration and we did not observe apnea in any of the patients in the propofol-ketamine group.

There was no incidence of bronchospasm or laryngospasm, cough or hiccups, in any of the groups, as both mixtures provided an adequate depth of anesthesia. Although ketamine was known to stimulate salivary secretions,[14] we did not encounter increased salivation in either group. This could be explained by the low dose of ketamine used in the mixtures in our patients.

The most commonly reported and unpleasant side effect associated with propofol administration was pain on injection. In our study there was no incidence of pain in the propofol-thiopentone group. With a prior injection of thiopentone 100 mg IV or when an admixture was used, there was less incidence of pain[15] and this effect was even better than with IV administration of 20 mg lignocaine.[16] There was no incidence of pain in the propofol-ketamine group either. This could be explained by the fact that ketamine antagonized the activation of N-methyl-D-aspartate (NMDA) receptors in the vascular endothelium or in the central nervous system (CNS), or it could be due to a combination of an addictive hypnotic effect, which diminished the pain sensation centrally.[10,17]

Co-administration of propofol with ketamine reduced the psychomimetic effects of ketamine.[7] In our

study, we found that only one patient had emergence delirium. This could be due to the dose-dependent interaction of excitatory anesthetic ketamine with a pure CNS depressant, such as, propofol or using midazolam as a premedicant or due to a lesser dose of ketamine administered when the admixture was used. There was no incidence of nausea or vomiting, as propofol was an antiemetic.[18,19,20]

In our study, the recovery time was significantly less in Group T as compared to Group K. Similar results were shown by Vora *et al*.[3] Gyorchynski *et al*.[21] showed that recovery time was shortened with propofol, as compared to ketamine. This was due to the fact that ketamine caused mood alterations, but the discharge times were comparable. This could be due to lesser concentrations of thiopentone and ketamine used in the admixture. Nausea and vomiting were not observed in any patient in the study. This could be explained by the use of propofol in both mixtures, which had antiemetic properties.[17,18,19] The antiemetic properties of propofol also translated in earlier discharge times in our patients.

The strengths of our study lie in the fact that it is a randomized and prospective study. We have noted two major limitations in our study. First, the drugs that we used have contrasting analgesic properties. Ketamine has intrinsic analgesic properties, whereas, thiopentone is an antanalgesic. In fact, our study demonstrates the value of adding an analgesic agent, in that, it deepens the anesthetic effect, as evidenced by a greater hemodynamic stability in Group K and lesser supplemental drug volumes required in Group K. The second limitation is the absence of a control group.

CONCLUSIONS

We conclude that both propofol-thiopentone and propofol-ketamine are good options in day-care gynecological surgeries rather using individual drugs, as both admixtures provided an adequate depth of anesthesia. The propofol-ketamine admixture has an edge over propofol-thiopentone in terms of hemodynamic characteristics. Moreover, the total dose of propofol required for the whole surgery in Group K was significantly less than that in Group T. Thus, the propofol-ketamine admixture may be a more economical option for patients, with lesser side effects, as compared to the propofol-thiopentone admixture.

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