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Comparison between Propofol and Ketofol (Ketamine and Propofol in the ratio of 1:1), during Colonoscopy for hemodynamic stability

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***Abstract*:**
Introduction: *In this study, we aimed to determine the proportion of ketamine-propofol (ketofol), in the ratio of 1:1, for colonoscopy procedures, to maintain the hemodynamic stability, in comparison with propofol alone.*
Material and methods: This is a prospective and randomized trial. The first group (group 1) was administered Ketofol (Ketamine 50mg and Propofol 50 mg), induction was performed, with 1 mg/kg propofol and 1 mg/kg ketamine. For the second group (group 2) induction was performed, with 2 mg/kg propofol. Additional doses of 0.5 mg/kg bolus propofol without ketamine were administered to both groups accordingly. The heart rate, mean arterial pressure (MAP), peripheral oxygen saturation values, colonoscopy period, adverse events, recovery time, discharge time, additional propofol doses, total propofol doses, colonoscopist and patient satisfaction were recorded.
Results: *In group 2, the MAP and heart rate mean was significantly lower than the initial and 3, 5 10 and 15 min readings.($p < 0.01$) Even at the end of the procedure, the differences between the two groups persisted. ($p<0.01$) and 10 mins after recovery the hemodynamic variables did not differ significantly between the two groups. There was no significant change in oxygen saturation. The mean total propofol dose of group 2 was significantly higher than group 1 ($p = 0.0001$). The mean colonoscopist satisfaction in group 2 was significantly lower than that in group 1 ($p = 0.047$).*
Conclusions: *In elective colonoscopy, a ketofol mixture prepared in the proportion 1: 1 provides suitable hemodynamic conditions and sufficient sedation with added analgesic effect.*
Key words: *colonoscopy, ketamine, propofol, ketofol.*

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I. Introduction

A colonoscopy is an outpatient procedure in which the inside of the large intestine (colon and rectum) is examined. A colonoscopy is commonly used to evaluate gastrointestinal symptoms, such as rectal and intestinal bleeding, abdominal pain, or changes in bowel habits. It is generally considered a highly invasive procedure that causes considerable discomfort to the patients Therefore, routine administration of sedative and analgesic drugs is widely provided for this procedure. Combination of benzodiazepines and opiates is the most common practice.

The sedative agents that are currently available for colonoscopy include midazolam, propofol, diazepam, diphenhydramine, promethazine, meperidine, and fentanyl. Among these, midazolam and propofol are the most commonly used sedatives, whereas fentanyl is the most frequently administered analgesic.

Consequently, multi-drug regimens exist including opioids, benzodiazepines, ketamine and propofol. Ketamine is a potent analgesic agent. Propofol is a strong hypnotic drug with short duration of action and more rapid recovery time for the patient compared with midazolam. Propofol is widely used for sedation. The fact that it acts rapidly and is short-acting is well-established, and it also has a dose-dependent hypotensive effect, due to decreased systemic vascular resistance and myocardial depression. Ketamine is a dissociative anaesthetic drug that has a stimulant effect on the cardiovascular system and preserves respiration [1]. The use of ketamine and propofol together can provide hemodynamic stability, also, the addition of ketamine reduces propofol consumption. Ketofol is a mixture of propofol and racemic ketamine in the same syringe; this combination is very popular for use in sedation and the induction of anaesthesia. [2]

There have been few studies directly comparing the combination of propofol and ketamine versus propofol alone for deep sedation in patients undergoing colonoscopy. There have been different practices in regards to the use of sedative agents. This study is designed to compare and evaluate the clinical efficacy of the

combination of propofol and ketamine (ketofol) versus propofol alone when each regimen is used as the sedative agents for deep sedation for colonoscopy procedures.

II. Material and Methods

After obtaining the approval of the ethics committee and the informed consent of the patients, a prospective, randomized study was undertaken of 30 outpatients, aged 18–60, ASA 1–2, scheduled to undergo elective colonoscopy in our Hospital. The study was completed in a 3-month period. The primary outcome of the study was to compare the advantages and efficacy of Propofol and Ketofol (Ratio of 1:1) for the colonoscopy procedure in terms of hemodynamic and sedation conditions. The secondary outcome of the study was to compare adverse effects, colonoscopist and patient satisfaction[3]. Prior to colonoscopy, the patients fasted for 8 hrs. Patients who were pregnant or who had anticipated airway difficulties and those who had current active GIS bleeding, severe cardiac and respiratory insufficiencies, an increase in intracranial pressure, a history of allergy to sedative medication, alcohol and drug addiction, and psychiatric disorders were excluded from the study. In all the patients, vascular access was achieved with an 18-gauge intravenous cannula, and fluid replacement was provided with a Ringer Lactate solution. To evaluate patient satisfaction, an oral scoring system on a scale of 1–10 was explained to the patients. For premedication, 1 mg midazolam was administered as standard to the patients. In the operation room, the values of peripheral oxygen saturation (SpO2), the non-invasive MAP (mm Hg), and the pulse rate (PR; beat/min) were recorded. With a Hudson Mask, 5 l/min O2 was given to the patients, who were assigned to the two groups according to their presentation at the hospital. The first group (group 1) was administered Ketofol (Ketamine 50mg and Propofol 50 mg, i.e. in the ratio of 1:1). The mixture was carefully titrated, and standard induction was performed, with 1 mg/kg propofol and 1 mg/kg ketamine. For the second group (group 2) a 200 mg propofol was prepared in 20 ml syringe (i.e. 10 mg /ml). The mixture was carefully titrated, and standard induction was performed, with 2 mg/kg propofol. After the process of colonoscopy had started, additional bolus propofol doses of 0.5 mg/kg were applied to both groups, without adding ketamine. The PR, MAP values and SpO2 values of the patients were recorded. 5 min after the beginning of the procedure and then at 1 min, 3min, 5min, 10 min and 15 min intervals until the end of the procedure. Additional propofol doses administered and the total propofol dose was calculated. Adverse events that developed during the process such as hypersensitivity reactions, bradycardia, tachycardia, hypotension, hypertension, respiratory depression, desaturation, nausea, vomiting, diplopia, bleeding and perforation were noted. The duration from stopping all anaesthetics to the time at which the patients were able to provide coherent answers to oral questions was accepted as the recovery time. The duration from the induction to the time at which the scores reached 9 or above according to the Aldrete recovery score was accepted as the discharge time. Patient satisfaction was scored by patients orally on a scale of 1 to 10 (0 = not satisfied, 10 = very satisfied) after recovery. Colonoscopist satisfaction was evaluated with a 10 cm visual analog scale[4,5].

III. Statistical Analysis

The descriptive statistical methods (mean, standard deviation) and one way/irreversible variant analysis were used in the repetitive measurements of the multiple groups. In the comparison of the sub-groups, the Newman-Keuls multiple comparison test was employed. In the comparison of the dual groups, the independent *t*-test was used, and in the comparison of the qualitative data, the c2 test and Fisher's exact test were used. The statistical significance level was set at $p < 0.05$.

IV. Results

There were no significant differences between the means of age, weight, duration of colonoscopy, gender and distributions of the ASA score of the 2 groups. There was also no statistically significant difference between the recovery time and the discharge time of the groups. The additional propofol dose mean of group 2 was statistically significantly higher than in group 1. The total propofol dose mean of group 2 was also statistically significantly higher than in group 1. Statistically, the mean colonoscopist satisfaction in group 2 was significantly lower than that of group 1.

Parameter	Group 1 (Ketofol group) (n = 15)	Group 2 (Propofol group (n = 15)	Value of p
Age [years]	48.85 ±9.96	51.08 ±11.76	0.364
Weight [kg]	74.3 ±15.54	76.5 ±14.49	0.514
Duration of Colonoscopy [min]	13.43 ±4.14	13.18 ±6.31	0.835
Male Gender Female	19 (47.50%) 21 (52.50%)	18 (45.00%) 22 (55.00%)	0.823
1 ASA score	21 (52.50%)	17 (42.50%)	0.370

2	19 (47.50%)	23 (57.50%)	
Recovery time [min]	3.75 ±1.98	3.38 ±2.26	0.433
Discharge time [min]	34.73 ±8.13	33.03 ±7.05	0.321
Additional propofol dose [mg]	32.5 ±7.07	49.5 ±18.29	0.001*
Total propofol dose [mg]	82.48 ±18.08	108.63 ±33.33	0.0001*
Colonoscopist satisfaction	9.6 ±0.67	9.25 ±0.87	0.047*
Patient satisfaction	9.63 ±0.63	9.38 ±0.77	0.117

**p < 0.05 (mean ± SD). ASA – American Society of Anesthesiologists.*

The preoperative hemodynamic parameters were studied, with no significant differences between the two groups. Even after ,1 minute after induction also there were no significant differences in hemodynamic variables between the two groups. But at 3 min, 5 min, 10min and 15 min post-induction, the heart rate and mean blood pressure grossly differ between the two groups, and there was no significant difference in SPO2. Both the parameters (HR and MBP) were decreased in the propofol group. This difference was highly significant ($p<0.01$). Even at the end of the procedure, the differences between the two groups persisted. ($p<0.01$) and 10 mins after recovery the hemodynamic variables did not differ significantly between the two groups.

Table: Heart rate means of group

Variable (Time)	Group 1 (Ketofol)	Group 2 (Propofol)	P Value
Preoperative	76.06 ±9.10	77.71 ± 8.47	0.47
1 min	79.63 ±9.14	78.03 ± 8.96	0.49
3 min	80.97 ±9.21	68.77 ± 9.56	<0.01
5 min	81.97 ±9.53	66.35 ± 8.04	<0.01
10 min	81.53 ±9.88	65.97 ± 8.33	<0.01
15 min	81.17 ±9.95	66.22 ± 7.24	<0.01
At the end of the procedure	80.03 ±9.89	67.29 ± 6.60	<0.01
10 mins after recovery	78.33±9.30	75 ± 7.23	0.13

Table: MAP means of group

Variable (Time)	Group 1 (Ketofol)	Group 2 (Propofol)	P Value
Preoperative	89.27±5.65	91.32±7.76	0.25
1 min	91.57±6.22	89.09±8.40	0.20
3 min	93.43±7.20	80.03±6.11	<0.01
5 min	93.87±6.64	78.32±6.71	<0.01
10 min	94.23±6.95	78.64±6.23	<0.01
15 min	93±8.69	79.06±6.69	<0.01
At the end of the procedure	93.5±7.39	81.97±7.93	<0.01
10 mins after recovery	89.33±6.62	89.48±9.09	0.94

Table: SPO2 means of group

Variable (Time)	Group 1 (Ketofol)	Group 2 (Propofol)	P Value
Preoperative	97.78 ±0.58	98 ±0.64	0.103
1 min	97.93 ±0.47	98.08 ±0.47	0.161
3 min	97.93 ±0.47	98.08 ±0.47	0.161
5 min	97.98 ±0.53	98.03 ±0.62	0.699
10 min	98.06 ±0.48	98.17 ±0.59	0.401
15 min	98.08 ±0.28	97.94 ±0.68	0.495
At the end of the procedure	98.33 ±0.58	98.25 ±0.46	0.808
10 mins after recovery	98.33 ±0.58	98.25 ±0.46	0.808

Adverse effect:

PONV: The incidence of PONV was very less in both groups. Only 1 patient in the Propofol group and 3 patients in the Ketofol group complained of nausea post operatively. Apnoea (complete cessation of respiration for 10 secs or more) was observed in 5 patients in the Propofol group and 1 patient in Ketofol group. Hallucinations were observed in 2 patients in the Ketofol group and no patients in the Propofol group. No other side effects like excessive salivation & secretions, laryngospasm, arrhythmias, muscular rigidity etc were observed in any of the patients in the study.

V. Discussion

In urgent and elective cases and for painful procedural sedation, the use of ketofol in different combinations have been recommended for both adults and children. One study showed that a ketofol mixture prepared in appropriate proportion provides optimal sedation and that it has explicit analgesic efficacy and a stabilizing impact in terms of haemodynamics in addition to removing the need for opioids. In our study, the

patients in group 1 were haemodynamically stabilized with the ketofol mixture prepared in the proportion 1: 1. In group 2, where we administered propofol, the MAP and heart rate is taken at 1, 3, 5,10 and 15-minute interval was lower than the ketofol group and there was no significant difference in SPO2. This hemodynamic difference was because of the 50% proportion of ketamine. Due to the additional propofol dose administered, the 15 min PR and MAP was significantly lower than the initial and

the 1 min. The additional propofol dose needed in group 2 was significantly higher than in group 1. Furthermore, while there was no difference between groups in terms of patient satisfaction in our study, the colonoscopist satisfaction was higher in group 1. We are of the opinion that this resulted from the better sedation conditions in group 1 despite lower application of additional propofol. These results lead us to the conclusion that ketofol prepared in the proportion 1: 1 is sufficient for colonoscopy, with more hemodynamic stability and added analgesic effect due to ketamine in the ketofol group.

Rapeport *et al.* used ketofol safely and effectively in four high-risk cases and stated that this technique had advantages such as analgesia, airway protection, provision of spontaneous respiration, hemodynamic stability, and rapid recovery. Another study compared propofol for procedural sedation in the emergency department with propofol-ketamine in terms of respiration depression and recovery time. It found that subclinical respiratory depression developed at a higher rate in the propofol group than in the ketamine group. More frequent awakening agitation was also observed in the ketamine group compared with the propofol group. The time to the return of the basal mental status was also longer in the ketamine group than in the propofol group.In another study that compared ketofol and propofol, the authors stated that although the group given ketofol experienced less explicit hemodynamic and respiratory problems, there was no difference between the two groups in terms of the need for active intervention, fluid-vasopressor support, supportive oxygen, or assisted ventilation. They also stated that in terms of discharge time, ketofol did not show superiority over propofol. The study also reported that the patients administered ketamine at higher doses had more nausea, vomiting, and recovery reactions after the operation. Phillips *et al.* stated that ketofol offers a valuable combination in procedural sedation and that compared to propofol it results in lower hypotension, better sedation quality, and improved patient comfort. In a comparison of ketofol and propofol by Andolfatto *et al.*, the authors stated that respiratory side effects, induction time, efficacy, and sedation time were similar but that the depth of sedation was more consistent with ketofol.

In our study, allergic reactions, desaturation, respiratory depression, and complications related to colonoscopy did not develop in any of the patients. However, in group 1, the rate of hemodynamic stability was much higher than in group 2. This was linked to the equal proportion of ketamine We also observed no differences between the groups in terms of dreaming, recovery time, and discharge time.

VI. Conclusion

In elective colonoscopy, a ketofol mixture prepared in the proportion 1: 1 provides suitable hemodynamic conditions and sufficient sedation with added analgesic effect. Thus, we suggest that a ketofol mixture prepared in the proportion of 1:1 is suitable for elective colonoscopy.

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