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Original Research Article

A Comparison of Thiopentone, Propofol and Combination of Ketamine-Propofol (Ketofol) as an Ideal Anesthetic Agent for Modified Electroconvulsive Therapy

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Abstract:

Background: Electroconvulsive therapy (ECT) is a widely utilized psychiatric intervention that involves the deliberate induction of seizures in patients using electrical stimulation, with the aim of producing therapeutic outcomes. Electroconvulsive therapy (ECT) has the potential to induce significant disruptions in the cardiovascular system, as well as a notable elevation in cerebral blood flow & intracranial pressure. The cardiovascular alterations might be modified with the use of different anaesthetic medications. The most often utilized induction drugs for electroconvulsive therapy (ECT) are Thiopentone and Propofol. In recent times, there has been an exploration of the use of Ketofol, a combination of Propofol with Ketamine, in the context of electroconvulsive therapy (ECT).

Aims and Objective: The purpose of this study was to conduct a comparative analysis of the impact of sodium Thiopentone, Propofol, and Ketofol as IV anaesthetic agents in modified electroconvulsive therapy (ECT). Specifically, the study aimed to assess the effects of these drugs on ECT-induced hemodynamic alterations, seizure duration, and recovery time.

Material and Methods: The study conducted was a prospective, randomized controlled trial that included a total of 90 patients aged between 18 and 60 years, who had ASA grade I and II and were scheduled to undergo electroconvulsive therapy (ECT). The patients in group T were administered Thiopentone at a dosage of 2.5 mg/kg, while those in group P received Propofol at a dosage of 1 mg/kg. Patients in Group K were administered inj. Ketofol, which is a combination of Inj. Propofol at a dosage of 0.5 mg/kg and Inj. Ketamine at a dosage of 0.5 mg/kg. The hemodynamic and recovery statuses of all groups were observed throughout the initial thirty-minute period. Additionally, data was collected on the length of seizures, the time it took for spontaneous eye opening to occur, the ability to respond to verbal commands, and agitation assessment scores.

Results: A statistically significant disparity in heart rate at 10 minutes and systolic blood pressure at 5 minutes was seen in the Thiopentone group (p-values of 0.008 and 0.011, respectively) following the administration of shock, in comparison to the other two groups. There were no statistically significant changes seen in seizure length, latency to spontaneous eye opening, and responsiveness to vocal commands ($p>0.05$). The group T exhibited the greatest mean agitation score (2.14 ± 0.56), as compared to both group P (1.64 ± 0.48) & group K (1.78 ± 0.64) ($P= 0.004$).

Conclusion: The hemodynamic stability of Propofol and Ketofol was shown to be superior to that of Thiopentone, whereas the seizure duration and recovery characteristics were equivalent among the three substances. Therefore, it can be concluded that both propofol and Ketofol exhibit effectiveness as induction drugs for electroconvulsive therapy (ECT), with propofol exhibiting a lower incidence of agitation compared to Ketofol.

Keywords: Electroconvulsive therapy; Hemodynamic; Ketofol; Propofol; Seizures; Thiopentone.

Introduction

Electroconvulsive therapy (ECT) is a therapeutic intervention for mental diseases that involves the administration of a controlled electric current to the brain of a patient who is under anaesthesia, utilizing specialized equipment. Muscle relaxants are capable of modifying convulsions. Electroconvulsive therapy (ECT) is widely regarded as a secure and highly efficacious intervention for several psychiatric conditions, including serious depression and catatonia.[1] Nevertheless, there is a prevalence of negative attitudes and misconceptions within the general population, as well as among medical students and even physicians. [2] This phenomenon mostly stems from a lack of knowledge and is subject to transformation via the acquisition of education and personal experience. The reasons behind the emergence of unfavourable opinions about ECT remain unclear.

However, there are several aspects that continue to be of concern in the anaesthetic management of electroconvulsive therapy (ECT), including the total period of anaesthesia, hemodynamic alterations, induction and recovery time and characteristics, interactions with antipsychotic medicines, as well as the influence on seizure duration and post-ECT disorientation. [3] Electroconvulsive therapy (ECT) has been associated with adverse effects including bradycardia and hypotension, subsequently followed by tachycardia and hypertension, as well as notable symptoms such as headache, myalgia, and agitation following the treatment. [4]

Thiopentone and propofol are two drugs that have been widely utilized in the context of electroconvulsive therapy (ECT). Thiopentone is linked to a number of adverse effects, including delayed recovery, increased risk of arrhythmias, laryngospasm, and a rise in seizure threshold. Additionally, its anti-convulsant function leads to a dose-dependent decrease in seizure length, which is not considered desirable in the context of electroconvulsive therapy (ECT). [5] Propofol has advantages such as rapid induction, seamless recovery, and minimal occurrence of post-procedural agitation. The hypotensive action of this substance is beneficial in mitigating the hypertension generated by electroconvulsive therapy (ECT).

However, it also leads to a reduction in seizure length, which is undesired during ECT, and this reduction is depending on the dosage of the substance. The use of Ketofol, a combination of ketamine and propofol, has emerged as a novel approach for the induction of electroconvulsive therapy (ECT) procedures. The hemodynamic stability is maintained by the equilibrium of cardiovascular characteristics shown by both propofol and ketamine. [7]

Numerous studies have been conducted in the past to examine the efficacy of Thiopentone versus propofol as induction drugs for electroconvulsive therapy (ECT). The efficacy of ketamine has also been evaluated in previous studies including electroconvulsive therapy (ECT). There is a scarcity of research on the use of Ketofol as an inducing drug in electroconvulsive therapy (ECT).

The purpose of this study was to conduct a comparative analysis of the impact of intravenous (IV) Thiopentone, Propofol, and Ketofol as IV anaesthetic agents in modified electroconvulsive therapy (ECT). Specifically, the study aimed to assess the effects of these drugs on ECT-induced hemodynamic alterations, seizure duration, and recovery parameters.

Aims and Objective: The purpose of this study was to conduct a comparative analysis of the impact of sodium Thiopentone, Propofol, and Ketofol as IV anaesthetic agents in modified electroconvulsive therapy (ECT). Specifically, the study aimed to assess the effects of these drugs on ECT-induced hemodynamic alterations, seizure duration, and recovery time.

Material and Methods

Following the approval of the institutional ethics committee (1656/Bio/ethics/MC) and obtaining informed consent, a prospective randomized double-blind study was carried out on a sample of 90 adults receiving medical treatment at an academic hospital that specialized in tertiary care in Central India.

Inclusion Criteria:

- Adult patients of either sex, of ASA grade I or II,
- Age group between 18-60 yrs
- Weights ranging from 40-70 kg,
- Scheduled for modified electroconvulsive therapy

Exclusion criteria:

The study excluded individuals who had a medical history of uncontrollable hypertension, type 2 diabetes, thyroid disorders, valvular heart disease, or bronchial asthma, as well as pregnant and lactating women. Patients who have a documented history of medication or food allergies were also not included in the study.

The patients were assigned into three separate groups of 30 each using computerised randomization.

Primary outcomes:

- To compare hemodynamic stability.
- To compare seizure duration.

Secondary outcomes:

- Time to spontaneous eye opening.
- Time to responding to verbal commands.
- Agitation scores.

The process of obtaining informed & written consent was carried out for both the patient and the patient's relative. The patients were instructed to abstain from oral intake for a period of 6 hours before undergoing electroconvulsive therapy (ECT). Additionally, they were permitted to maintain their prescribed antipsychotic medication regimen until the morning of the procedure. The participants were allocated into three distinct groups of equal size, consisting of 30 individuals each, by the use of the sealed envelope technique. Patients in group T received Thiopentone 2.5 mg/kg, group P received Propofol 1 mg/kg, while patients in Group K received inj. Ketofol, a combination of Inj. propofol 0.5mg/kg + Inj. ketamine 0.5mg/kg. To ensure the integrity of the study, the patients were maintained in a state of blinding by the use of the sealed envelope technique. Additionally, the observer anesthesiologist was deliberately kept unaware of the specific medicine administered to each patient, in order to mitigate the potential influence of observer bias. The anesthesiologist responsible for administering the research medicines did not participate in any subsequent aspects of the trial.

In the electroconvulsive therapy (ECT) room, the process of intravenous cannulation was performed, followed by the initiation of an infusion of ringer lactate (RL). The basal parameters, including heart rate (HR), mean blood pressure (MBP), systolic blood pressure (SBP), and diastolic blood pressure (DBP), were documented.

The administration of intravenous Glycopyrrolate at a dosage of 0.004 mg/kg was employed as a premedication strategy. The vital parameters, including blood pressure (BP), heart rate (HR), and peripheral oxygen saturation (SPO2), were recorded. Following a duration of 2 minutes, the patient was administered the designated research medication and further observations were made about their hemodynamic characteristics.

To examine the duration of seizure activity, a sphygmomanometer cuff was inflated to 100mmHg beyond the systolic blood pressure, isolating one of the upper limbs. Following the isolation of the limb, a dosage of 0.75 mg/kg of succinylcholine was administered. Manual ventilation was then conducted utilising Bain's circuit, utilising 100% oxygen at a flow rate of 8L/min. In order to prevent potential harm to anatomical tissues within the patient's mouth cavity, a bite block was employed. During the surgery, an electrical stimulation over the threshold level was administered using bi fronto-temporal electrodes, and oxygen was provided to aid with respiration. The length of the seizure, which refers to the period starting from the delivery of the shock to the termination of tonic-clonic motor activity in the limb that was "isolated," was documented. The systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), and peripheral oxygen saturation (SpO2) were measured at time intervals of 0, 5, 10, 15, and 20 minutes following the administration of the shock. The patients were administered 100% oxygen till the restoration of spontaneous respiration. The duration of time required for the eyes to open and the duration of time required for the individual to comply with verbal commands were also recorded. In cases where patients reported experiencing symptoms of nausea and vomiting, the administration of intravenous Ondansetron at a dosage of 4mg was implemented. The evaluation of post-recovery agitation was conducted by employing an emergence agitation score. [8]

Statistical analysis:

The data was reported in the form of mean ± standard deviation (SD). The demographic data were subjected to analysis using the Chi-square test to determine any associations or relationships. Additionally, the analysis of variance test was employed to assess the statistical significance of differences in means. The frequency and percentage were computed using SPSS 17 software. A significance level of <0.05 was deemed as statistically significant, while a significance level >0.05 was regarded as statistically non-significant.

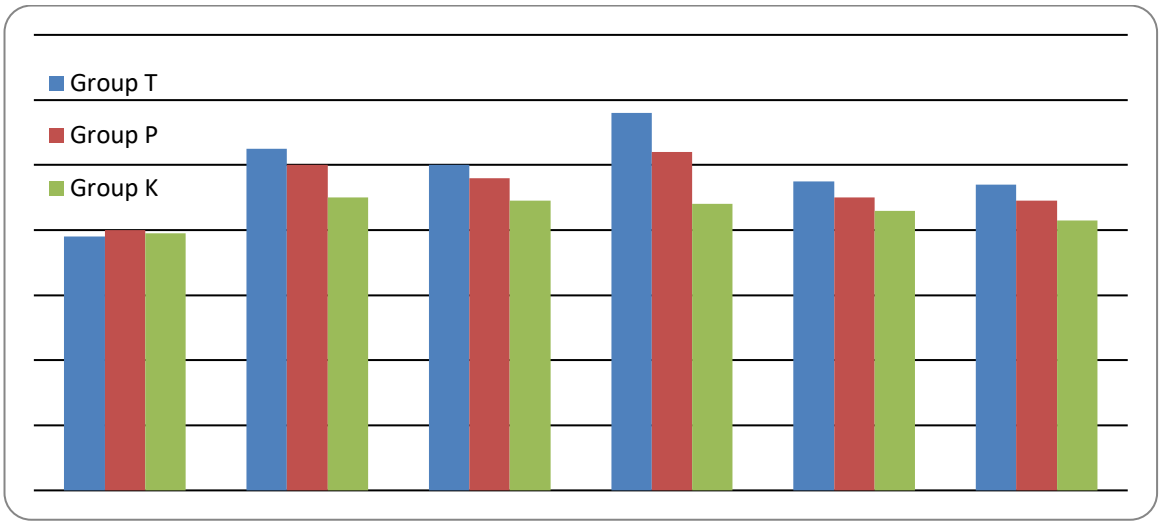
Results

The average age of the patients included in the present research was 31.63 ± 10.19. Similarly, the average weight of the patients was 56.53 ± 12.50 Kg. The gender distribution among the patients was 57% male and 43% female. The pre-operative (baseline) vital measures, including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP), were found to be similar across all the groups ($p > 0.05$). (Table 1)

Table 1: Comparison of the baseline (pre-induction) parameters in the two groups

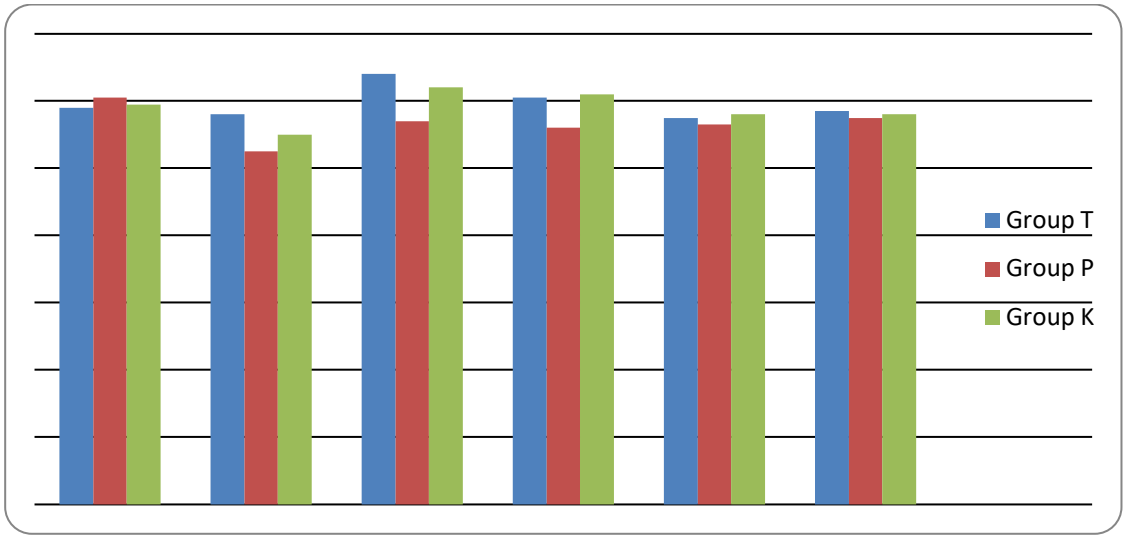
Variable	Group-T	Group-P	Group-K	p-value
SBP (mmHg)	118.32±9.36	121.30±8.32	119.43±8.56	0.32(NS)
DBP (mmHg)	76.32±8.34	78.12±7.36	77.25±7.72	0.42(NS)
HR (bpm)	78.36±6.02	80.34±7.23	79.42±6.34	0.30(NS)
SPO2	98.01±1.02	97.23±0.98	97.67±0.99	0.21(NS)

NS- Not Significant. Following the delivery of premedication, namely the injection of Glycopyrrolate, there was an observed rise in heart rate across all three groups. A further elevation in heart rate was noticed subsequent to the administration of the electrical shock. The propofol group had a lower percentage rise in heart rate compared to the Ketofol and Thiopentone groups. A statistically significant disparity in heart rate was seen at the 10-minute mark following the administration of a shock in the study groups. Specifically, group T exhibited greater heart rate values in comparison to groups K and P (p = 0.008). (Graph 1)



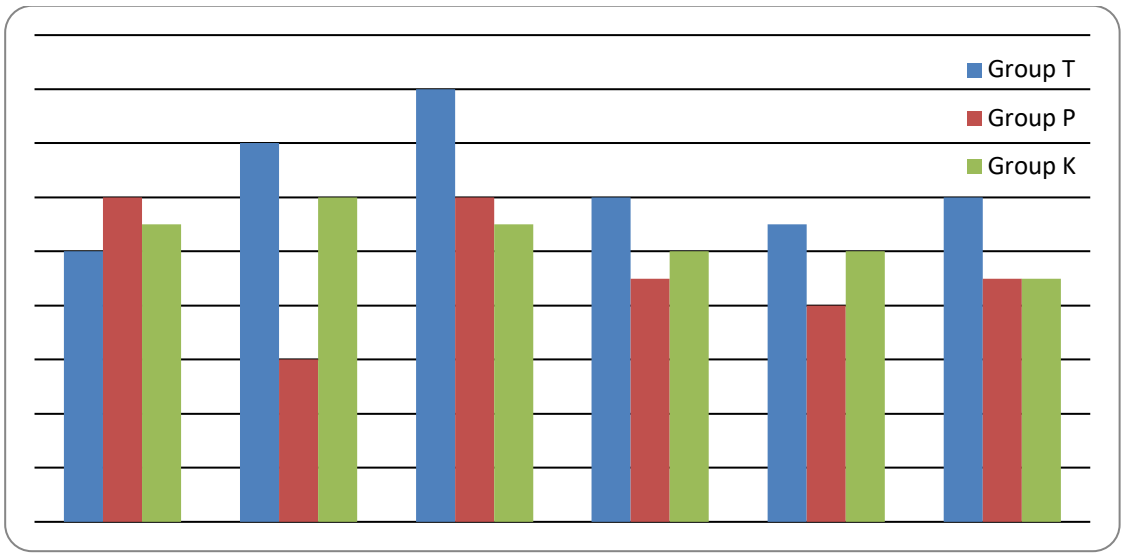
Graph 1: Comparison of mean heart rate at different time interval in three groups

Following the delivery of the study medicine, Group P exhibited a statistically significant reduction in mean systolic blood pressure (SBP) compared to the baseline measurement, with a decrease of 4.84%. Conversely, Group K has shown a statistically non-significant decrease of 1.13% in SBP, while Group T displayed a non-significant increase of 3.66% in SBP. All of the research groups exhibited a statistically significant rise in systolic blood pressure (SBP) following the administration of a shock stimulus (P <0.05). A statistically significant difference was seen in systolic blood pressure (SBP) after 5 minutes following the application of shock. Group T exhibited a higher SBP value compared to groups K and P (p = 0.011).



Graph 2: Comparison of systolic blood pressure (SBP) at different time interval in three groups

A statistically significant difference in diastolic blood pressure (DBP) was seen following the delivery of the study medication and immediately after the shock. Specifically, group T exhibited a greater DBP value compared to groups K and P ($P < 0.05$).



Graph 3: Comparison of diastolic blood pressure (DBP) at different time interval in three groups

The average duration of seizures seen in Group T (30.78 ± 12.80) was found to be longer when compared with Group P (24.85 ± 10.72) & Group K (25.88 ± 12.25).

However, it is important to note that this difference was not statistically significant. The duration required for spontaneous eye opening ($p = 0.431$) and the duration needed to comply with spoken orders ($p = 0.265$) were found to be similar across all three groups. An agitation score greater than 2 was seen in 10% of patients in the Ketofol group and 23.33% in the Thiopentone group.

All patients in the propofol group did not exhibit an agitation score greater than 2. The mean agitation score exhibited the greatest value in Group T (2.13 ± 0.57), which demonstrated a statistically significant difference when compared with Group P (1.63 ± 0.49) & Group K (1.77 ± 0.63) (P=0.003).

Table 2: Comparison of seizure duration and recovery parameters in three groups

Variables	Group-T (Mean±SD)	Group-P (Mean±SD)	Group K (Mean±SD)	p-value
Seizure duration (seconds)	38.77±12.80	24.85±10.73	25.89±12.26	0.127 (NS)
Spontaneous eye opening time	5.07±2.38	4.21±2.82	4.81±2.68	0.432 (NS)
Time to obeying verbal commands	7.27±2.68	5.91±3.72	6.34±3.37	0.266 (NS)
Mean Agitation score	2.14±0.56	1.64±0.48	1.78±0.64	0.004 (HS)

Discussion:

Electroconvulsive treatment (ECT) utilizes electrically generated generalized seizures as a therapeutic intervention to alleviate symptoms associated with mental diseases, such as severe depression, mania, and schizophrenia. Additionally, it is employed as a supplementary intervention in cases where the patient exhibits an inadequate response to medication.[11]

While the administration of anaesthetic agents can effectively mitigate physical and psychological distress, it is important to acknowledge that these medications can also elicit undesirable consequences such as nausea, vomiting, dizziness, headache, and sleepiness. These unpleasant effects have been shown to last for a considerable duration beyond the medical intervention. The administration of barbiturate anaesthesia has the potential to enhance the amnesic impairments caused by electroconvulsive therapy (ECT) specifically for nonverbal material. The administration of anaesthesia has been found to be correlated with an increased likelihood of falls and the potential for fractures. This association can be attributed to the effects of dizziness, drowsiness, and psychomotor impairment induced by anaesthetic agents.[12,13] Ensuring the appropriate level of anaesthesia is crucial during the process, while also emphasizing the significance of achieving sufficient seizure length to provide the desired therapeutic outcomes. Hemodynamic instabilities, such as the occurrence of bradycardia that is followed by tachycardia and hypertension, have been seen in association with electroconvulsive therapy (ECT), posing potential

challenges for individuals with heart conditions. An optimal inducing chemical should effectively mitigate the hemodynamic instability associated with electroconvulsive therapy (ECT) while also maintaining the length of the seizure without any compromise. The anticonvulsant activity of Thiopentone sodium, an extremely short acting barbiturate, may have a negative impact on the length of seizures. Propofol has vasodilatory effects, which contribute to enhanced hemodynamic stability during electroconvulsive therapy (ECT). However, it also exerts a suppressive influence on seizure activity due to its potent anticonvulsant properties. Ketamine has the potential to induce cognitive or behavioral disruptions, such as post-procedural psychosis. On the other hand, the antidepressant properties of this treatment contribute to the enhancement of the clinical results of electroconvulsive therapy (ECT). The use of ketamine during electroconvulsive therapy (ECT) leads to an increase in seizure length, mostly attributed to its limited anticonvulsant effects.[9,19] However, it is possible that the administration of Ketamine might worsen the occurrence of tachycardia and hypertension that are commonly observed during Electroconvulsive Therapy (ECT). [18-20]

Ketofol, which is a combination of propofol and ketamine, is a recently introduced induction drug that is being utilized in electroconvulsive therapy (ECT). The combined effects of both medications contribute to a reduction in the dosage of each drug in the cocktail, therefore leveraging the advantages associated with forgetfulness, analgesia, and hypnosis. The combination of propofol and ketamine offers a favourable edge in maintaining hemodynamic stability due to the balancing impact they have on one other's hemodynamic properties. The concurrent administration of propofol and ketamine has been seen to mitigate the occurrence of hallucinations commonly associated with ketamine usage. [21] The administration of ketamine has been seen to negate the anticonvulsant effects of propofol, hence leading to an improvement in seizure duration when these two drugs are used in combination. [22]

During electroconvulsive therapy (ECT), the administration of induction drugs is often performed at slightly reduced doses in order to mitigate their impact on the length of seizures. Upon conducting an extensive review of the available literature, it was discovered that the typical induction dosages of Thiopentone, Propofol, and Ketamine in electroconvulsive therapy (ECT) range from 2 to 4 mg/kg, 0.75 to 2 mg/kg, and 0.7 to 2.8 mg/kg, respectively. In the current investigation, a combination of pharmaceutical substances was employed. Specifically, a dosage of 2.5mg/kg of Thiopentone, 1mg/kg of Propofol, and a mixture consisting of 0.5mg/kg of ketamine combined with 0.5mg/kg of propofol, referred to as Ketofol, were administered. The dosages employed in our study align with those utilized by Omprakash et al. [15] and Erdogan et al. [19] in their separate investigations.

According to a research conducted by Shah et al. [13], there is a notable prevalence of gag reflex, coughing, and vomiting among those who are administered Thiopentone during induction. The observed phenomenon was not evident in the investigation conducted. The administration of propofol through injection resulted in discomfort at injection in 20% of the patients, whereas thrombophlebitis occurred in 3.3% of the patients. However, the occurrence of such adverse effects was non-existent in our study.

In their study, Manjula et al. [17] noticed a substantial increase in heart rate at 1, 2, 3, 5, and 10 minutes after electroconvulsive therapy (ECT) as compared to the baseline data. The findings of our research align with the outcomes of their investigation. Erdogan and colleagues [19] did a study in which they used Ketofol and propofol as part of their experimental protocol. The study demonstrated a notable increase in heart rate at time points T0 and T5 in the propofol group, whereas in the Ketofol group, heart rate was found to be greater than the first measurement at T0 and lower than the initial measurement at T1. The absence of anticholinergic premedication resulted in the lack of sustained elevation in heart rate.

In the conducted study, a reduction in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) was seen in group P following the administration of the study medicine. Following the administration of a shock, there was a statistically significant rise in blood pressure seen across all three groups. However, the percentage increase was found to be the lowest in group P and the largest in group T. Additionally, it was observed that the blood pressure readings returned to their initial levels sooner in group P compared to groups K and T.

In a research conducted by Erdogan et al. [19], the effects of Ketofol (0.5/0.5) and propofol (1mg/kg) on systolic blood pressure (SBP) were examined. The results indicated that both study groups saw a comparable rise in SBP when compared to their respective baseline values. However, the comparison between the two groups revealed a significantly lower increase in the propofol group ($P < 0.05$). In their study, Mir et al. [23] conducted a comparison of Thiopentone, propofol, and etomidate as induction drugs for electroconvulsive therapy (ECT). The study demonstrated an increase in systolic blood pressure (SBP) following the administration of a shock stimulus, which persisted

for duration of two minutes. Subsequently, a declining pattern in SBP was observed beyond the two-minute mark. The observed variability in the Thiopentone group exhibited statistical significance. The group administered with propofol had a lesser increase in comparison to the first measurement. In their investigation, Jaitawat et al. [24] investigated the effects of propofol (1.5mg/kg), etomidate (1.5mg/kg), and Ketofol (ketamine 0.8mg/kg + propofol 1.5mg/kg) on systolic blood pressure (SBP) at various time intervals in comparison to the baseline. The results of their study did not reveal any statistically significant differences in SBP between the aforementioned drugs and the baseline measurements.

This finding contradicts the results of our investigation. The utilization of elevated dosages of propofol and ketamine in their research may have potentially influenced this observed disparity. Erdogan and colleagues [19] observed a statistically significant increase in diastolic blood pressure (DBP) at all time periods in the Ketofol group when compared to the baseline values ($P = 0.001$). The study found that the DBP levels were significantly greater at T0, T1, T3, and T5 in the Ketofol group compared to the propofol group ($P < 0.029$). In their study, Mir et al. [23] reported a statistically significant increase in diastolic blood pressure (DBP) following the administration of a shock, which persisted for up to 2 minutes across all experimental groups ($P < 0.05$). Nevertheless, there was a notable increase in the Thiopentone group, which was statistically significant. The findings of our investigation are consistent with the results of both of these aforementioned studies.

According to existing research, it has been found that electroconvulsive therapy (ECT) does not yield therapeutic benefits when the produced seizure activity lasts for <25 seconds. [26] In our investigation, we noticed a mean seizure length of at least 25 seconds in all patients. The findings reported by Erdogan et al. [19] and Manjula et al. [17] exhibit similarities with the results obtained in our investigation. Saban et al. [25] observed a significantly shorter duration of seizures in the propofol group compared to the Ketofol group ($P < 0.01$). A larger dosage of ketamine was employed during the formulation of Ketofol.

This factor might perhaps have been a contributing factor to the extended duration of seizures observed in the Ketofol group. In their investigation, Hashem et al. [27] reported a significantly longer seizure duration in the Thiopentone group compared to the propofol group ($P = 0.001$). The use of an increased dosage of propofol and a decreased dosage of Thiopentone in their investigation may have potentially influenced their findings, therefore presenting a contradiction to the outcomes seen in our own study. No statistically significant differences were seen in the recovery metrics across the three groups. Erdogan and colleagues [19] Saban et al. [25] and Bodkhe et al. [28] reported similar recovery characteristics in the Ketofol/propofol and propofol/Thiopentone groups, respectively.

In contrast, Jaitawat et al. [24] noticed a shorter duration of spontaneous eye opening and latency to comply with vocal directions in the propofol group comparison to the Ketofol group. The administration of a larger dosage of propofol & ketamine in the Ketofol group may have potentially resulted in a delayed recovery.

The prevalence of post-electroconvulsive therapy (ECT) delirium has been documented to vary between 3.23% and 18%. [21] There is a paucity of literature research that have examined post-electroconvulsive therapy (ECT) agitation while simultaneously evaluating the effects of different induction agents. Both of Thiopentone and ketamine have been found to potentially contribute to an increased occurrence of post-procedure agitation, while propofol has been seen to have the lowest incidence of agitation.

In their investigation, Butterfield et al. [29] noticed a decrease in cognitive impairment during the initial recovery phase following electroconvulsive therapy (ECT) when propofol was used as an anaesthetic agent, as compared to Thiopentone anaesthesia. Our observations align with the findings of their investigation. The administration of Ketofol entails the counterbalancing of the effects of ketamine by the use of propofol. Therefore, the occurrence and intensity of agitation are also reduced in comparison to the administration of ketamine alone. In a study conducted by Tarek et al. [30], it was reported that 8.6% of patients in the Ketofol group had an agitation score >2. The results of our investigation align with these findings.

Limitations:

Ideally, the monitoring of seizure duration during electroconvulsive therapy (ECT) should involve the simultaneous use of electroencephalogram (EEG), a practice that was not implemented in our study. In addition to this, the monitoring of anaesthesia depth using BIS monitoring was not feasible. A research design that included the administration of induction drugs at a dosage level sufficient to achieve a comparable depth of anaesthesia would have provided a more comprehensive assessment of hemodynamic parameters.

Conclusion

The current study found that Propofol (1mg/kg) and Ketofol (a combination of Propofol 0.5mg/kg + Ketamine 0.5mg/kg) resulted in improved

hemodynamic stability and reduced post-procedural agitation compared to Thiopentone (2.5mg/kg). Therefore, it can be inferred that both Propofol and Ketofol can be utilized as efficient inducing drugs in patients undergoing electroconvulsive therapy (ECT), despite the fact that propofol is linked to a lower incidence of post-procedural agitation in comparison to Ketofol.

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