International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 13, No. 9, September 2024 Online ISSN: 2250-3137
Print ISSN: 2977-0122

DOI: 10.69605/ijlbpr_13.9.2024.21

ORIGINAL RESEARCH

A Randomised clinical trial to compare effectiveness of ketofol and ketofol-dexmedetomidine group in patients undergoing modified electroconvulsive therapy

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Received Date: 16 July, 2024 Acceptance Date: 20 August, 2024

ABSTRACT

Introduction: Over time, the use of ketamine and propofol in electroconvulsive therapy (ECT) anaesthesia has increased. This study assessed the impact of dexmedetomidine prior to ketofol, a ketamine and propofol combination, circulation dynamics, the duration of seizures, the emergence agitation post-ECT, and the recovery period.**Methods:** We randomly assigned 60 ASA (American Society of Anesthesiologists) class I or II patients scheduled for ECT to two groups: the ketofol (KF) and the ketofol-dexmedetomidine (KFD), each with thirty patients. The groups received 0.5 mcg/kg dexmedetomidine and 10 ml of 0.9% saline infusion intravenously for at least 10 minutes and 10 minutes prior to the procedure, respectively, before administering ketofol. We studied the duration of the seizures, the circulatory dynamics before, during, and after ECT, and the effects on agitation, depression, mania, and psychosis. We also identified early and post-Modified E.C.T. complications.**Results:** In both groups, demographic profiles regarding age and gender showed no significant results. Most of the patients in group KFD reached their target MAP (mean arterial pressure) and HR (heart rate) faster and with less hemodynamic fluctuation than those in group KF. This was due to lower induction doses of ketofol (KFD > KF) and shorter induction times (KFD > KF). The mean Hamilton Depression Rating score was significantly lower in the KFD group compared to the KF group.**Conclusion:**Dexmedetomidine given before electroconvulsive therapy (ECT) helps stop immediate hyperdynamic reactions and lowers agitation after the procedure without changing the length of the seizure.

INTRODUCTION

Modified electroconvulsive therapy (ECT) is a well-researched treatment for numerous mental illnesses, but substantial side effects like cardiovascular stress and cognitive impairment can upset patients. To reduce such adverse effects and improve patient outcomes, appropriate anaesthetic management during ECT is essential. ECT was first used in 1938. Electroconvulsive therapy (ECT) is a procedure in psychiatry where patients are electrically charged in an attempt to alleviate mental disease symptoms. Transcutaneous electrodes provide electricity to the cortex, causing a tonic-clonic seizure lasting 10-15 and 30-60 seconds [1]. Bipolar disorder accounts for 70% of ECT patients, and schizophrenia for 17%. This method replaces medication seizure therapy easily and effectively [2]. A seizure duration of less than 15 secs is ineffective, and more than 120 sec achieves less favourable responses to ECT. Initially, inadequate muscle relaxation during ECT led

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to bone fractures, joint dislocation, tongue biting, and muscle fibre tears. An acute cardiovascular response and a generalized motor seizure result from applying electrical current to the brain. This leads to severe cardiac issues, most commonly a brief period of hypertension, fluctuations in heart rate (HR), and a significant increase in blood flow to the cerebral tissue [3]. Physical and psychological trauma caused to the patient with unmodified direct ECT in the past is now modified with anaesthesia [3]. Anaesthesia in ECT serves multiple purposes: it reduces the anxiety and discomfort associated with the procedure, ensures patient immobility to prevent injury, and modulates the hemodynamic responses triggered by the induced seizures. Traditionally, a combination of agents has been used to achieve these goals, focusing on balancing sedation, analgesia, and hemodynamic stability. Ketamine, a dissociative anaesthetic, has gained popularity in recent years for its rapid onset and potent analgesic properties, making it a suitable candidate for ECT anaesthesia. However, ketamine alone can cause psychomimetic effects and hypertension, prompting the need for adjuncts that can counteract these drawbacks. Propofol, known for its sedative and antiemetic properties, is frequently combined with ketamine to form a mixture known as ketofol. This combination aims to leverage the benefits of both agents while minimizing their respective side effects in a variety of procedural circumstances, including ECT; ketofol has been demonstrated to offer efficient sedation and analgesia with a favourable hemodynamic profile. However, an ongoing search exists to optimize this regimen to enhance its efficacy and safety further. Dexmedetomidine, an alpha-2 adrenergic agonist, has emerged as a valuable adjunct in anaesthesia and sedation protocols. Its effects include analgesia, sedation, and anxiolysis without causing a noticeable respiratory depression. Moreover, dexmedetomidine has been noted for its ability to provide stable hemodynamics and reduced stress response, making it an attractive candidate for inclusion in ECT anaesthesia protocols. When combined with propofol, hallucinations and the hyperdynamic response of ketamine are mitigated [4]. Ketamine, when used with propofol, reduces the amount of propofol needed and helps maintain hemodynamic stability. Ketamine propofol sedation results in a shorter recovery period on average than intravenous ketamine alone but a more extended recovery period than intravenous propofol alone. As a result, premedication with dexmedetomidine during ECT needs to be assessed in terms of circulation dynamics and seizure duration [5]. The impact of this combination on patients' post-ECT agitation and depression can also be evaluated.

MATERIALS & METHODS

The institutional ethics committee of our tertiary care facility (B.L.D.E.U.) approved our study (BLDE(DU)/IEC/778 2022-23). Trial registration number: CTRI/2023/09/057361, Clinical Trial Registry of India.

Study design: A randomized clinical trial.

Randomisation: A digitally generated sequence was used for randomisation on procedure day. Group allocation was concealed via sealed envelopes. Based on group assignment, solutions were prepared by a nurse who wasn't part of the study. We have also followed the CONSORT (Consolidated Standards of Reporting) guidelines in our study (Figure *1*).

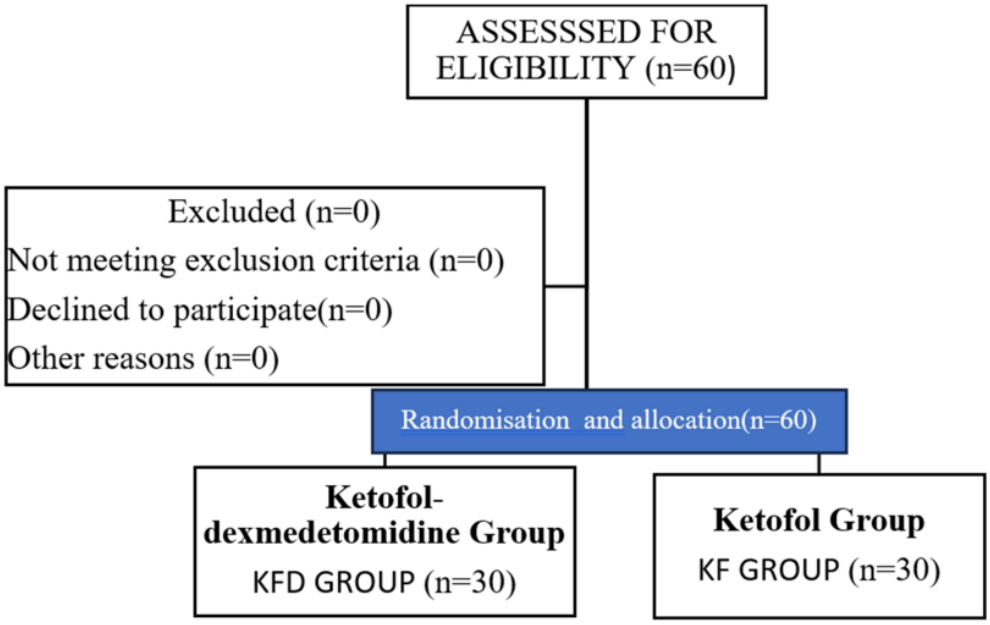

Figure 1: RANDOMISATION AND ALLOCATION

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Inclusion and exclusion criteria

Patients of either sex, ages eighteen to sixty, scheduled for ECT (Electroconvulsive Therapy) under general anesthesia and with an American Society of Anaesthesiologists (ASA) class I or II participated in the study.

This study excluded patients with cardiovascular illness, cerebrovascular condition, intracranial hypertension, pulmonary disease, glaucoma, pacemaker, prior history of seizures, ASA III-V physical status, study drug allergy, or pregnancy.

A pre-anesthetic evaluation was done in the ward. The procedure was explained to the patient attendees, and informed consent was obtained from them. We conducted a pre-ECT cognitive assessment using the Mini-mental State Examination (MMSE), assessed the severity of psychiatric illness using the Hamilton Depression Rating Scale (HAM-D), the Young Mania Rating Scale (YMRS), and the Positive and Negative Syndrome (PANSS) scale, and also assessed the pre-MECT agitation score. For six hours of overnight fasting, patients were kept nil by mouth. Patients were connected to the baseline monitors to continuously monitor their heart rates, electrocardiogram, non-invasive blood pressure, and oxygen saturation (Spo2). Parameters were noted at baseline, after induction, during ECT, and after 5, 10, and 30 minutes after the end of the seizure. An IV connection was made. Groups, respectively, received 0.5 mcg/kg dexmedetomidine (diluted with 0.9% saline up to 10 ml) and 10 ml of 0.9% saline infusion intravenously for not less than 10 minutes and 10 minutes prior to the procedure. Later, each patient received 0.5 mg of intravenous atropine sulfate as a premedication in both groups. For three minutes, patients were pre-oxygenated with 100% oxygen. Subsequently, both groups were given ketofol (10 mg/ml of ketamine + propofol each in a 20-ml syringe) at a 1:1 ratio; gradually (2 mg/sec) until they lost their ability to respond when their name was called aloud and their eyelash reflex disappeared. Additional ketofol in 10 mg increments was given if the recipient's verbal response was not lost within 60 seconds. We noted both the total induction time and the necessary total dose of ketofol. We administered 0.5 mg/kg of succinylcholine after inducing anesthesia. We provided assistant ventilation with oxygen (8 L/min) and performed manual ventilation. A bite block was inserted. We administered a suprathreshold electrical stimulation using bifronto-temporal electrodes. We then ventilated the patients using a face mask with oxygen (14–18 breaths/min) until they recovered clinically from the state of anesthesia. The time interval between the start of E.C.T. and the end of tonic-clonic motor activity in the "isolated" arm was used. The recovery period was documented using Aldrete's score of ≥9.

Statistical analysis

After entering the data into an Excel sheet from Microsoft, we analyzed it using social science statistical software (Version 20). Mean±SD, median, interquartile range, frequency, percentages, and graphs were used to present results. We compared two groups using an independent t-test for normally distributed continuous variables and a Mann-Whitney U test for non-normal variables. We compared the categorical variables of the two groups using the Chi-square test. $p<0.05$ was considered statistically significant. Every statistical test was two-tailed.

RESULTS

The mean age and sex distribution between the groups ketofol (KF) and ketofol- dexmedetomedine (KFD) were analysed using (t-test), and results are statistically not significant, and were comparable between the groups as shown in the (Table1).Time to consciousness (7.26 ± 2.63 min vs 6.32 ± 1.26 min); obey command (12.62 ± 4.91 min vs 10.94 ± 2.93 min) orientation (22.34 ± 5.97 min vs 18.63 ± 6.42 min) ability to sit unaided (23.94 ± 3.94 min vs 20.71± 4.29 min) time taken to meet discharge criteria105.23 ± 6.97 min vs 62.31± 8.46 min) were not significantly higher in ketofol group compared to ketofol-dex group respectively.

Table 1: Patients' demographic data

Parameter	KFD	KF	p-value
Age(years, mean±SD)	41.23 ±3.64	39.8 ± 4.24	0.166
Male/female	23/7	25/5	0.518

SD: Standard DeviationKFD= ketofoldexmedetomedine group
KF=ketofol group

Mean duration of motor seizure (Sec) were was longer in KFD compared to KF (28.57 ± 2.32 in KFD , 22.43 ± 1.00 in KF with P-value<0.001) with a minimum acceptable hemodynamic fluctuation, reduced induction dosages of ketofol (54.07 ± 3.11 in KFD , 81.30 ± 2.36 in KF with P-value<0.001), and a shorter induction times (40.21± 4.62 in KFD , 52.32±6.24 in KF with P-value<0.001).Mean induction time in KFD group was earlier than group KF (Table 2) .

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Table 2: Induction time (sec), duration of motor seizure(sec) and Induction dose (ketofol) in gm

Parameter	KFD	KF	p-value
Induction Time (Sec)	40.21 ± 4.62	52.32±6.24	<0.0001
Duration of Motor Seizure (Sec)	28.57 ±2.329	22.43 ±1.006	< 0.001
Induction Dose (Ketofol in gm)	54.07±3.11	81.30±2.36	<0.0001

Results are shown as mean (± SD) with **p-value<0.01, indicating highly significance at 5% level.
KFD= ketofoldexmedetomedine group
KF=ketofol group
SD= standard deviation

Compared to group KF, the majority of patients in group KFD achieved their goal MAP in KFD group : 91.23 ± 1.04 ,88.77 ± 1.47 ,93.20 ± 1.91 ,90.80 ± 2.56 ,86.30 ± 1.70 ,85.63 ± 0.92 and in KF group : 91.73 ±1.46,91.80 ±1.06,107.93± 1.53,98.07 ±1.11,98.33± 1.06,95.97 ± 1.21 at baseline, after induction during ECT 5,10,30 min post ECT respectively (Figure 2). Mean arterial pressure after induction till 30 minutes were statistically highly significant.

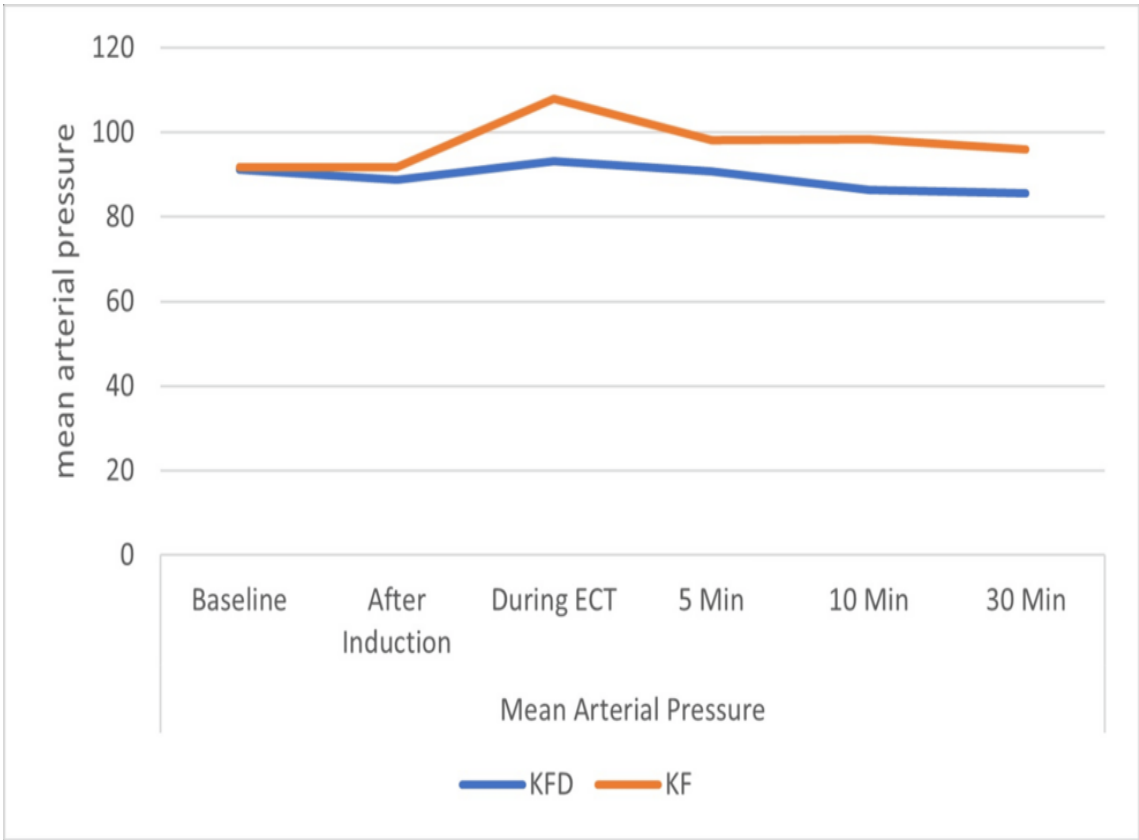

Figure 2: Mean arterial pressure between the groups.

Results are presented as mean (± standard deviation) with a significance level set at $p < 0.05$.
MAP= Mean Arterial Pressure KFD= Ketofoldexmed Group
ECT= Electroconvulsive Therapy KF= ketofol Group

MAP in KFD group : 91.23 ± 1.04 ,88.77 ± 1.47 ,93.20 ± 1.91 ,90.80 ± 2.56 ,86.30 ± 1.70 ,85.63 ± 0.92 and in KF group : 91.73 ±1.46,91.80 ±1.06,107.93± 1.53,98.07 ±1.11,98.33± 1.06,95.97 ± 1.21 at baseline, after induction during ECT 5,10,30 min post ECT respectively.
Mean heart rate HR in KFD group :76.5±5.62 ,75.62±5.12 , 89.66±3.40, 73.42 ± 5.91, 72.61 ± 6.81, 73.62 ± 4.5 and in KF group : 77.24 ± 6.24, 103.8 ± 9.14 ,104.8 ± 7.02, 105.8 ± 3.92, 76.91 ± 6.24 ,77.26 ±6.21 at baseline, after induction during ECT 5,10,30 min post ECT respectively (Figure 3). Mean heart rate after 5 minutes, induction and ECT till 30 minutes were statistically significant. KFD had smaller mean heart rate fluctuations than KF.

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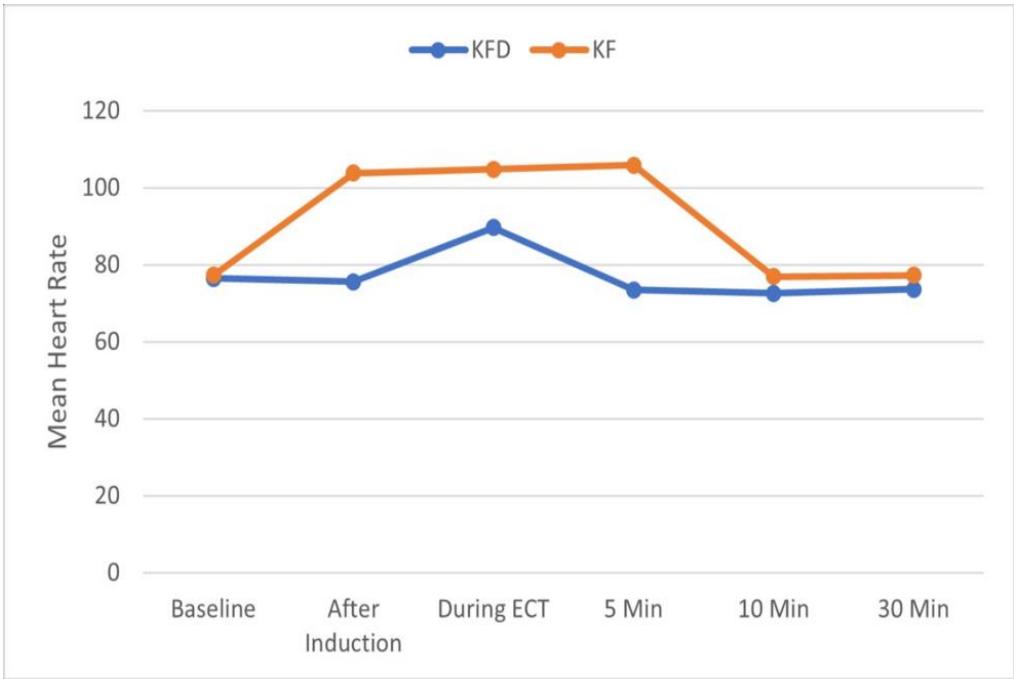

Figure 3: Mean heart rate between the groups

Results are presented as mean (± standard deviation) with a significance level set at $p < 0.05$.

HR= Heart rate (mean) KFD= Ketofoldexmed Group

ECT= Electroconvulsive Therapy KF= ketofol Group

HR in KFD group :76.5±5.62 ,75.62±5.12 , 89.66±3.40, 73.42 ± 5.91, 72.61 ± 6.81, 73.62 ± 4.5 and in KF group : 77.24 ± 6.24, 103.8 ± 9.14 ,104.8 ± 7.02, 105.8 ± 3.92, 76.91 ± 6.24 ,77.26 ±6.21 at baseline, after induction during ECT 5,10,30 min post ECT respectively. HR= heart rate, ECT=Electroconvulsive Therapy

Mean oxygen saturation between the groups during induction (p=0.005),and after 10 minutes (p=0.033) and 30 minutes (p=0.0313) were statistically significant, but during ECT (p=0.3618) and at baseline (p=0.6489) it was comparable. Richmond agitation sedation scale, showed that 22 patients were found alert and calm in group KFD while there were 14 patient found alert and clam. In group KF, there were 8 patients were found agitated while in the same group 7 patients were found with restlessness and only 4 patients were found with restlessness. Each of 2 patients were found with drowsiness and had light sedation and only 1 patient was with drowsiness in group KF(Figure 4).

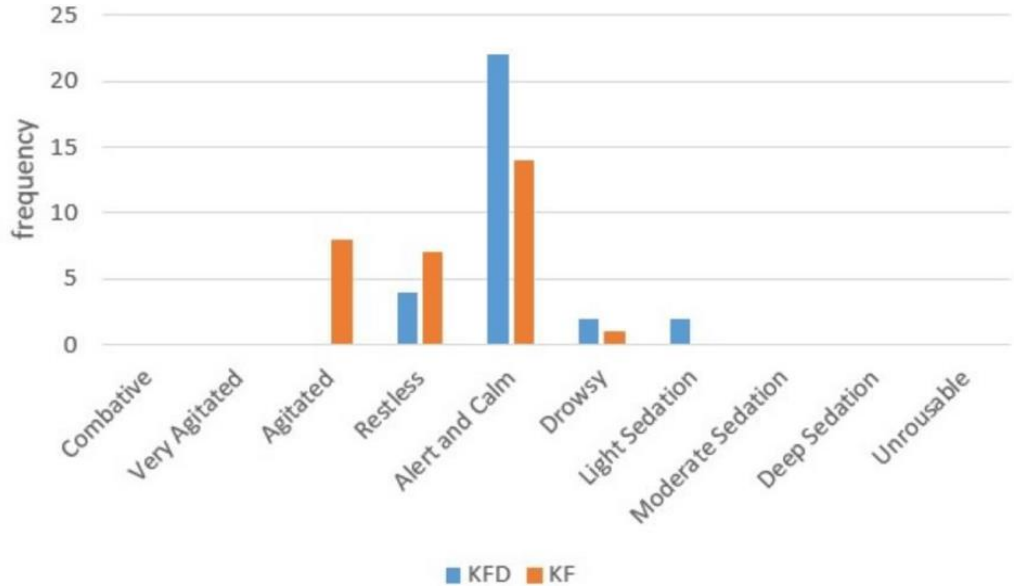

Figure 4: Richmond Agitation sedation scale between the groups.

KFD= Ketofoldexmed Group KF= Ketofol Group

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DISCUSSION

ECT (Electroconvulsive Therapy) is a highly recognized, well-accepted, and efficacious therapy technique for a variety of psychiatric conditions. In 1951, Wanderdel developed modified ECT using succinylcholine. It reduces the incidence of physical and psychological trauma [6]. Given that it preserves cognitive function and has an antidepressant effect, ketamine appears to be a suitable anesthetic for ECT [7].

Cardiotoxicity, brief psychotic episodes, and delayed recovery are among the side effects of ketamine [8]. Ketamine inhibits norepinephrine re-uptake in peripheral nerves and heart tissue, as well as catecholamine release into the bloodstream [9]. Furthermore, propofol could balance out the effects of ketamine on nausea and psychomimetic behavior [10]. A number of antihypertensive medications have not been able to totally stop the hypertension response post-ECT stimulation without producing persistent low BP recordings, according to earlier research [11].

Dexmedetomidine reduces the need for anesthesia and postoperative analgesics, blunts the hemodynamic response to intubation and operation, and provides intraoperative hemodynamic stability, as multiple studies have shown [12, 13]. Its sedative effect helps to reduce agitation and improve satisfaction in patients [14].

The ketofol with dexmedetomidine (KFD) has also lowered agitation and produced an acceptable hemodynamic response, all without causing any serious adverse effects [10]. Age (p-value=0.166) and gender (p-value=0.518) variations between groups were statistically insignificant and comparable. KFD had a statistically significant earlier mean induction time than the ketofol (KF) group (40.21 sec vs. 52.32 sec).

Roopesh Kumar et al. [15] found that for group A (KFD), overall seizure length improved (35.13 ± 1.48) compared to group B (KF) (31.04 ± 3.46) without impacting recovery. Our investigation found that KFD had a statistically significant longer mean motor seizure (Sec) duration than KF. Previously, experts recommended ECT for seizures lasting more than 25 seconds. [16]. According to reports, the only seizures that can lead to a reduced therapeutic benefit are those that are abortive or very brief (15 s). [17].

The mean heart rate after 5 minutes of induction, ECT, and 30 minutes was statistically significant, although comparable during induction. KFD had a lower mean heart rate than KF. The difference in mean arterial pressure from induction to 30 minutes was also statistically significant. The KFD group exhibited a lower mean arterial pressure than the KF group, in line with the findings of Z. Begec et al. Another study by Garg K et al. demonstrated that dexmedetomidine significantly reduced post-ECT hyperdynamic reactions compared to the control group.

According to the study Z Begec et al., since ECTs are usually performed as outpatient procedures, the anesthetics utilized should have quick recovery times. According to another study by X. Li et al., ECT procedures are outpatient procedures that need anesthetic agents with rapid recovery profiles [18]. The study group KF had earlier time for consciousness compared to the KFD group and was statistically significant. Infusing a lower dose of dexmedetomidine could eventually help patients recover faster, lowering their chance of experiencing a delayed recovery.

After 1 day to 5 days, the mean Hamilton depression rating score between the groups showed lower incidence in group KFD and higher in group KF, with a statistically significant difference between the groups. Our findings align with the research by Mizrak A, Koruk S et al., indicating that premedication with dexmedetomidine and midazolam reduces agitation following electroconvulsive therapy.

Another research effort by Shams et al. investigated the effects of the ketofol-DEX combination on depression and agitation during electroconvulsive therapy (ECT). The results showed that the mixture increased patient satisfaction, decreased depression and agitation, and reduced blood pressure and heart rate in an appropriate amount of time. Their results agreed with what we noticed. The mean MMSE scores before and 2 hours after ECT are not statistically significant between KFD and KF groups. JasmeinObbelset al.'s study revealed that ECT significantly improved patients with a Mini-Mental State Examination (MMSE) score of less than 24. In contrast, patients with MMSE scores (≥24) did not change significantly [19].

Similarly, mean Positive and Negative Syndrome Scale (PANSS) scores in schizophrenia patients before and after ECT are not statistically significant between the two groups, wherein 3 out of 8 patients with schizophrenia have shown a slight decrease in their negative symptoms.

Limitation

We limited our study to our institution and only included patients classified as ASA I and II. Dexmedetomidine is a useful non-opioid drug. However, patients with bradycardia and hypotension should use it cautiously, as the medication may exacerbate these findings. We did not assess the serum potassium levels. As SCh can lead to adverse effects like hyperkalemia, it is crucial to do so in patients with comorbidities. We did not use Electromyography (EMG) to assess fasciculation. Standard guidelines may require studies involving multiple institutions to consider dexmedetomdine as a premedication for electroconvulsive therapy.

CONCLUSIONS

Based on our observations, results, and references to other studies, we can say that the combination of

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ketofol and dexmedetomidine for ECT leads to longer mean seizure time and a good drop in heart rate and blood pressure compared to ketofol, with no major side effects. Also linked to a slightly effective anti-depressant effect and a lower incidence of agitation, these data suggest that premedication with dexmedetomidine may be useful in preventing the acute hyperdynamic responses to ECT.

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