



A COMPARATIVE CLINICAL STUDY OF PROPOFOL AND THIOPENTONE SODIUM AS INDUCTION AGENTS DURING ADMINISTRATION OF ELECTROCONVULSIVE THERAPY

KEY WORDS:

Dr. (Col) Mustafa Kapadia

PROF

Dr. Tanya Chhuda\*

PG-3 \*Corresponding Author

Dr. Sadhana Sanwatsarkar

PROF. & HOD

Dr. Kamal Kishor Patel

PG-3

ABSTRACT

INTRODUCTION: Electroconvulsive therapy (ECT) is a well-established psychiatric treatment in which seizures are electrically induced in patients for therapeutic effects. ECT can produce severe disturbances in the cardiovascular system and a marked increase in cerebral blood flow and intracranial pressure. These cardiovascular changes may be altered using various anaesthetic drugs.

AIMS AND OBJECTIVES:- The study was undertaken to compare Thiopentone sodium and Propofol as induction agent for modified ECT, to evaluate their effects on duration of seizure, hemodynamic changes, recovery time, and immediate complications.

MATERIALS AND METHOD:- The study was conducted on 100 patients undergoing modified ECT. All the patients underwent pre anaesthetic check-up, kept nil by mouth 6 hours prior to ECT. They were premedicated with glycopyrrolate (0.2 mg I.V. 15 minutes before), preoxygenated (100% oxygen by Bain circuit), given either Thiopentone sodium (2.5mg/Kg I.V.) or Propofol (0.8 mg/Kg I.V.) and succinyl choline (0.5 mg/Kg I.V.). After bite block insertion and stabilisation of joints, ECT was administered and duration of seizure activity, recovery time, pulse rate, blood pressure, respiratory rate, SpO2, ECG changes, immediate complications were noted for one hour post ECT.

RESULT:- It was found that patients who received Propofol had less variation in heart rate, blood pressure, early recovery, less post ECT complications as compared to those who received Thiopentone sodium.

CONCLUSION-Propofol is a better induction agent for ECT than Thiopentone sodium.

INTRODUCTION

Prior to 1930, available options for the treatment of psychiatric ailments were limited and a sort of custodial care was provided to these patients to prevent self-inflicted or accidental injuries. Later on hydrotherapy, cold therapy, prolonged sleep therapy, insulin coma, scotch douches etc were in use. With these methods of treatment outcome remained doubtful.

In (1934)<sup>1, 2</sup> Meduna, mistakenly, hypothesized that epilepsy has protective effect on symptoms of psychiatric illness. His clinical trials with intra muscular Camphor and Leptazol confirmed it.

Later on Fink (2001, 2004)<sup>1</sup> emphasized that it is not the cause of epilepsy, but the grandmal seizure occurring are antagonistic and symptoms of psychiatric illness are diminished. He called this as 'Biological Antagonism'.

In the year (1937)<sup>3</sup> Ugo Cerellete, a neuropsychiatrist and Leuci Binni found that convulsions can be more easily induced with electric current when compared with chemicals and drugs. Thereafter electric current became an established practice to induce convulsions. This treatment was called Electro Convulsive Therapy (ECT).

Availability of antipsychotic and antidepressant drugs in 1950's was favoured against electro convulsive therapy for the ease of administering treatment. These drugs like Barbiturates, Bromides, Paraldehyde and Chloral Hydrate provided variable results.

During the period of 1940-50, use of unmodified electro convulsive therapy received negative reporting in media and was another reason for disfavoring ECT. Unmodified ECT caused terrifying grand mal convulsions which resulted in musculoskeletal injuries, paralysis, sudden cardiac arrest and respiratory obstruction on several occasions.

After re-establishment of therapeutic value of electrically induced convulsion in treatment of psychiatric ailment, major innovations occurred in administering ECT in the coming years, that included brief pulsed current, unilateral application of ECT, use of anaesthesia, oxygenation, use of muscle relaxants, EEG seizure monitoring etc. and avoidance of excessive amount of sine wave current, and bilateral application of ETC.

Electro Convulsive Therapy administered with sedation, anaesthesia and muscle relaxants was named Modified Electro Convulsive Therapy (MECT). Use of anaesthetic agents provided brief period of amnesia during application of electric current; muscle relaxants decreased the intensity of muscular contractions and use of oxygen during brief period of respiratory depression avoided damages due to oxygen lack; pre-medication with anticholinergics like atropine or glycopyrrolate to prevent reflex changes in cardiac rhythm and decrease secretions.

Many hospitals in our country do not have proper anaesthesia facilities and services of qualified anaesthesiologists. It is suggested by Andrade C, Reie K, Sutharsthan R and Shah N (2000) and Pearlman T, Loper M, Tillery L (1990)<sup>4</sup>, that even if services of qualified anaesthesiologists are not available, psychiatrist himself should administer some sedative/hypnotic drug to these patients before ETC.

The essential elements of anaesthesia for electro convulsive therapy include-

- A) Rapid loss of consciousness.
- B) Effective attenuation of hyper dynamic response to electrical stimulus.
- C) Avoidance of gross muscle movements.
- D) Minimum interference with seizure activity.
- E) Prompt recovery of spontaneous respiration and consciousness.

F) Pain and anxiety control in post ictal period.

World Health Organization (1960) and Government of India in Mental Health Care Bill 2010 decided that, direct ECT will not be used any longer and health ministry recommended a ban on direct ECT, since then all electroconvulsive treatment are carried out under sedation or anaesthesia, using muscle relaxants for control of crude muscle movements.

Methohexital - an ultra-short acting barbiturate is the "gold standard" against which all other drugs used for the purpose are compared. Since Methohexital was not available, other drugs like Pentothal sodium were in use. Now Propofol is employed because of its recovery profile. Both drugs have anticonvulsant effect, hence careful selection of dose is paramount for favourable outcome of ETC.

In the present study we used commonly available anaesthetic agents/sedative in operating rooms namely Thiopentone sodium and Propofol with sub-paralytic dose of Succinyl choline to find out quality of anaesthesia provided by them.

**MATERIALS AND METHOD**

The study was conducted on 100 adult patients of either sex scheduled to undergo modified electro convulsive therapy (ECT) for various psychiatric conditions under general anaesthesia.

Patients included in the study were divided in two groups namely P and T to receive Propofol or Thiopentone sodium respectively.

At the time of pre anaesthetic check-up patient's relatives were informed to keep the patient nil by mouth 6 hours prior to the procedure. An informed written consent was obtained from the relatives of the patients.

On arrival in the ECT/ Operating room, intra venous infusion access was obtained and secured, and monitors were attached to record electro -cardiogram, non-invasive blood pressure, respiratory rate, SpO<sub>2</sub> and heart rate continuously throughout the procedure.

All patients on each sitting were pre medicated with injection Glycopyrrolate 0.2 mg intravenously 15 minutes before the procedure and pre-oxygenation with 100% oxygen was carried out at tidal breathing for 5 minutes using Mapelson D breathing circuit.

All the patients included in the study received anaesthetic agent as per their group assignment. Group T patients received injection Thiopentone sodium at 2.5mg/kg dose I.V and Group P patients received injection Propofol at 0.8 mg/kg dose I.V

All patients received injection succinyl choline chloride 0.5 mg/kg dose or maximum of 50 mg.

Ventilation was assisted on Bain circuit with 100% oxygen till disappearance of fasciculations and after that bite block was inserted, patient positioning and stabilization of joints was done. Head band was placed 2.5 to 4 cm above the mid-point of an imaginary line joining lateral canthus of eye and tragus (bilateral temporal). Frequency of 50 Hz, pulse width 1.2 mS, current 700mA was selected. Electric current was delivered bilaterally, duration of which was selected according to the patient and details were recorded.

On cessation of muscle contractions respiration was assisted with 100% oxygen till return of spontaneous breathing.

Duration of seizures was recorded in seconds.

Duration of time to recovery was assessed by a single measure, asking the patient to open his or her eyes at 1-min interval and recording the time from the end of the injection of the initial dose of induction agent until spontaneous movements and response to verbal commands was first obtained.

After completion of procedure patients were shifted to post anaesthesia recovery room in lateral position for further observation for an hour.

**OBSERVATIONS AND RESULT**

The ECT administrations were analysed on 100 patients belonging to ASA Grade 2 of physical status without symptoms and signs of systemic diseases. The data on study parameters were recorded in a pre-designed case record proforma and tabulated.

In this study both the groups had similar demographic profile. Table 1 shows the mean age of the patients included in the study. Table 2 shows distribution of patients according to sex. Table 3 shows distribution of patients according to weight.

Age Group (Years)	Group T	Group P
Mean Age (Years)	34.78	32.02
Standard Deviation	12.161	9.947
p value	0.22	

**Table 1**

Sex	Group T	Group P
Male	27	36
Female	23	14

**Table 2**

Weight(Kg)	Group T	Group P
Mean weight(Kg)	62.32	64.42
Standard Deviation	15.518	14.330
P value	0.49	

**Table 3**

Amongst the indications for administering ECT to patients, most common was schizophrenia (42%), followed by bipolar mood disorder (34%). Other indications were amotivation syndrome/major depressive disorder (5%), acute transient psychosis (4%), body dysmorphic disorder (4%), delusional disorder (3%), obsessive compulsive disorder (3%), personality disorder (3%), mixed anxiety disorder (1%) and post psychotic depression (1%).

Frequency of 50 Hz, pulse width 1.2 mS, current 700mA was selected in the ECT machine. The duration of shock delivered varied for patients and it was recorded. The machine delivered energy depending upon the head impedance of patient. Table 4 shows the mean duration of current delivered was 4.732+0.668 seconds in group T and 4.732+0.436 seconds in group P. It was similar in both groups.

Duration in seconds	Group T	Group P
Mean duration (in sec)	4.732	4.732
Standard Deviation	0.668	0.436
p value	1.00	

**Table 4**

Table 5 shows duration of seizure in each group. The mead duration of seizure activity observed in group T was 21.46+ 8.132 sec and in group P was 22.86+ 6.324. It was not statistically significant (p value=0.34)

Seizure duration in seconds	Group T	Group P
0 – 15 sec(very short)	13	9
15 – 120 sec(adequate)	37	41
> 120 sec(very long)	0	0
Mean duration of seizure	21.46	22.86
Standard Deviation	8.132	6.324
p value	0.34	

**Table 5**

Figure 1, bar diagram shows time taken to recover i.e follow commands in each group. For group T average time to recover was 9.5+3.257minutes whereas for group P patients it was 5.88+2.916 minutes being significantly less than the former(p value=0.00).

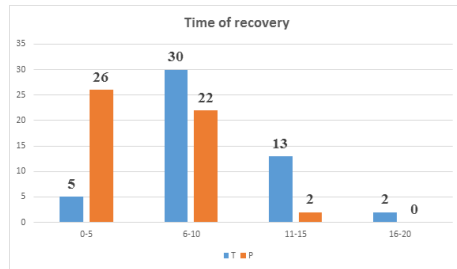


Figure 1

Figure 2, line diagram shows the pulse rate recorded at different times of procedure. Mean pulse rate was recorded at pre-induction, immediately post induction and at 2.5, 5, 10, 15, 30, 45 and 60 minutes after the delivery of MECT. Mean pulse rate was significantly different for group T and P patients at 2.5 minutes. The mean pulse rate for group T was  $117.6 \pm 21.26$  and for group P patients the mean pulse rate was  $103.96 \pm 23.48$ . Statistical analysis revealed these changes to be significant ( $p = 0.00$ ).

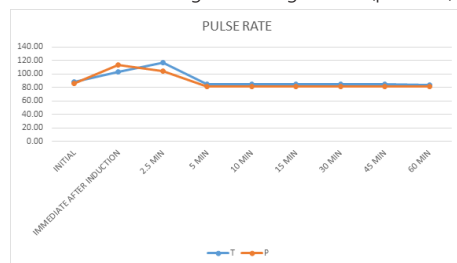


Figure 2

Figure 3, line diagram shows the changes in systolic blood pressure. It is seen that significant difference in systolic blood pressure was seen at 2.5 and 5 minutes of observations between the two study groups T & P. Mean Systolic blood pressure observed was  $151.36 \pm 24.91$ ,  $134.36 \pm 18.90$  for group T patients. For group P patients the values observed were  $133.96 \pm 21.27$ ,  $124.90 \pm 13.60$ . P value calculated were 0.00, 0.01 respectively.

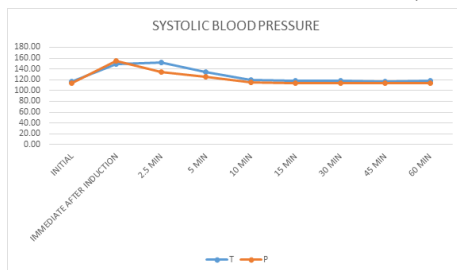


Figure 3

Figure 4, line diagram shows the changes in diastolic blood pressure. It is seen that significant difference in diastolic blood pressure was seen at 2.5 and 5 minutes of observations between the two study groups T & P. Mean Diastolic blood pressure observed was  $94.38 \pm 11.28$ ,  $85.56 \pm 11.85$  for group T patients. For group P patients the values observed were  $88.06 \pm 10.81$ ,  $81.18 \pm 9.23$ . P value calculated were 0.01, 0.04 respectively.

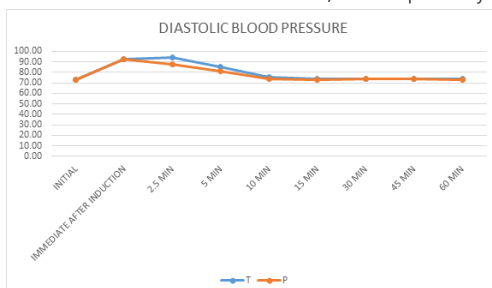


Figure 4

Figure 5, line diagram comparison of percentage saturation of hemoglobin with oxygen is shown for both groups. Although at all times of observation and most occasions percentage saturation of hemoglobin remained within clinically acceptable limits. The difference observed was not statistically significant at any time interval.

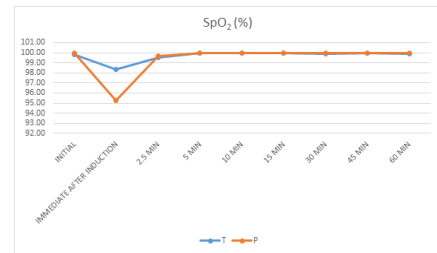


Figure 5

Figure 6, line diagram comparison of respiratory rate is shown for both groups. The difference observed was not statistically significant at any time interval.

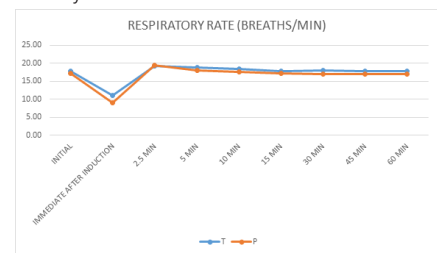


Figure 6

The ECG changes observed post ECT are transient and most of them spontaneously revert back to sinus rhythm without any treatment. In group T, 8 patients had sinus bradycardia immediately after ECT, 29 had sinus tachycardia. 37 patients had sinus tachycardia 2.5 minutes after ECT. 3 patients had VPC, 1 had irregular heart rate, 1 had VT and 1 had ST segment depression. In group P, only 2 patients had sinus bradycardia, 36 had sinus tachycardia immediately after ECT. 1 patient had VPC and 1 had VT.

The following complications were observed in the patients for which some rescue maneuver was used. 2 patients in group T had episode of hypertension where systolic BP was more than 200mmHg, whereas only 1 patient in group P had systolic blood pressure more than 200mmHg. 2 patients had an episode of desaturation in group T and only one patient got desaturated in group P. In group T, 3 patients had VPC >6/min and one patient had an episode of VT where as in group P one patient had episode of VT which after treatment by inj loxicard (1.5mg/Kg) IV converted to VPC and later subsided. 1 patient in group T had sinus bradycardia that required treatment with Inj. Atropine 0.6mg IV and 1 patient had ST segment depression whereas no patient had sinus bradycardia or ST segment depression in group P. In group T, 3 patients had episode of vomiting and 3 patients were irritable in post ECT period in PACU (post anaesthesia care unit) whereas none had vomiting and only 2 patients were irritable in group P.

The following rescue maneuvers were- 2 patients in group T and 1 patient in group P received 1 puff of Nitroglycerin sublingually (400mcg/dose from metered dose spray) for hypertension. 2 patients had an episode of desaturation, 1 had ST segment depression in group T and only 1 patient got desaturated in group P. 100% oxygen was given by intermittent positive pressure application by bag and mask using Bain circuit. In group T, 3 patients had VPC >6/min and 1 patient had an episode of VT. They received Inj. Loxicard (1.5mg/Kg) IV. In group P 1 patient had episode of VT which after treatment by Inj. Loxicard (1.5mg/Kg) IV converted to VPC and later subsided. 1 patient in group T had sinus bradycardia that required treatment with Inj. Atropine 0.6mg IV. In group T, 3 patients had episode of vomiting, for which they

received Inj. Ondansetron 4mg IV whereas none had vomiting in group P. 3 patients of group T and 2 of group P became irritable in PACU post ECT and received Inj. Midazolam 1mg IV.

## DISCUSSION

The ideal anaesthetic used for electroconvulsive therapy should have characteristics that include rapid induction, shorter duration of action, minimal side effects, rapid recovery, and no interference with electroconvulsive therapy efficiency<sup>5</sup>. The findings of our study are discussed below.

Amongst the indications for administering ECT to patients, most common was schizophrenia (42 patients), followed by bipolar mood disorder (34 patients). In the study conducted by Manjula BP et al.<sup>5</sup>, the maximum number of patients presented with the diagnosis of severe depression (24%) and schizophrenia (14%). In the study conducted by Boey et al.<sup>6</sup> in 1990, the most common conditions for which patients received electroconvulsive therapy were schizophrenia and severe depression.

In present study all patients were pre medicated with injection Glycopyrrolate 0.2 mg intravenously 15 minutes before the procedure.

The induction dose of Propofol in this study is 0.8 mg/kg. It is less than the dose used by Manjula BP et al.<sup>5</sup> for Propofol i.e. 1.2 mg/kg. The dosage of Propofol used by Simpson et al. was 1.3 mg/kg and Boey et al.<sup>6</sup> in 1990 was 1.33 mg/kg. Kadoi et al.<sup>7</sup> in 2000 used Propofol in doses of 1 mg/kg and Fredman et al.<sup>8</sup> 0.75 mg/kg, which is less than the present study. Mulier et al.<sup>9</sup> had used Propofol at a dose of 1.4 mg/kg. The dosage of Propofol used by Gazdag et al.<sup>10</sup> was 1 mg/kg in 2004.

The dosage of Thiopentone sodium used by Manjula BP et al.<sup>5</sup> and Moacyr A Rosa et al.<sup>11</sup> in 2008 was similar to our study i.e. 2.5 mg/kg.

Succinyl choline chloride (0.5-1.5 mg/Kg) is the preferred muscle relaxant for ECT to modify seizures and prevention of musculo-skeletal injuries, due to its shorter duration of action and fast action<sup>12</sup>. In present study, dose of succinyl choline used was 0.5mg/kg. Manjula BP et al.<sup>5</sup> used succinyl choline in doses of 0.6 mg/kg.

The duration of shock delivered was similar in both groups ( $p > 0.05$ )

In present study, patients who received Thiopentone sodium, 37 patients had seizure activity lasting for optimal duration. Whereas in patients who received Propofol, 41 out of 50 patients had seizure activity that lasted for optimal duration. In study conducted by Manjula BP et al.<sup>5</sup> the results were similar to our study, i.e. it showed no statistically significant change in seizure duration when either Propofol or Thiopentone were used. (Propofol group- 35.84±6.12 seconds and Thiopentone sodium group- 36.78±6.55 seconds). The mean duration of seizure in the Propofol group was 37.5 seconds as recorded by Boey et al.<sup>6</sup> in 1990.

The time taken to recover i.e. follow verbal commands for group T was 9.5±3.257minutes whereas for group P patients it was 5.88±2.916 minutes being significantly less than the former ( $p$  value=0.00). This result concurred with the conclusions found by Moacyr A. Roas et al.<sup>11</sup> in 2008 where, the recovery time with Propofol (1-1.5 mg/Kg) and Thiopentone (2-3 mg/kg) were 7.4 min and 9.4 min, respectively. In the study conducted by Manjula BP et al.<sup>5</sup>, mean recovery time for Propofol group was 7.36 ± 1.02 min and Thiopentone group was 8.48 ± 1.23 min. Fredman et al.<sup>8</sup> in 1994 concluded that cognitive recovery with Propofol was more favourable.

ECT leads to marked transient bradycardia immediately, sometimes even brief period of asystole that last for several seconds (parasympathetic effect) in the absence of anticholinergic premedication. This is rapidly followed by tachycardia. The mean pulse rate increased from the baseline values in both the groups

immediately after giving ECT, however the increase in rate was significantly more in Thiopentone sodium group as compared to Propofol. The heart rate reached the baseline values within 5 minutes in both the groups. Manjula BP et al.<sup>5</sup> found that the heart rate changes following Propofol were significantly lower than following Thiopentone sodium at all times after electroconvulsive therapy. The mean change in the heart rate after electroconvulsive therapy varied 30-40 beats/min above the baseline values with Thiopentone while the mean change in the heart rate observed with Propofol was only 10-20 beats/min above the baseline value within the first 3 min followed by a decrease in the heart rate gradually to baseline values in the next 2 min.

In the present study, it was observed that both systolic and diastolic blood pressure raised post ECT, however it was significantly more for Thiopentone group. Boey et al.<sup>6</sup> in 1990 studied 32 patients undergoing electroconvulsive therapy who had administered 1.25 mg kg-1 of 1% Propofol and 2 mg kg-1 of Thiopentone sodium and observed that the systolic blood pressure and diastolic blood pressure of both groups increased above the preanaesthesia baseline values significantly after electroconvulsive therapy. The increase in the systolic blood pressure and diastolic blood pressure were greater with Thiopentone sodium. Kadoi et al.<sup>7</sup> in 2001 reported the systolic blood pressure and diastolic blood pressure changes using Propofol 1 mg kg-1, which were the same as in our study. In the study conducted by Manjula BP et al.<sup>5</sup>, the rise in systolic blood pressure after 1 min of electroconvulsive therapy was 21.28 ± 0.06 mmHg with Propofol and 42.27 ± 3.87 mmHg with Thiopentone anaesthesia. In the Propofol group, the fall in systolic blood pressure was very rapid and systolic blood pressure reached the preanaesthesia value by 5 min after electroconvulsive therapy. In the similar way, the diastolic blood pressure increased more in the Thiopentone group as compared to the Propofol group and reached the baseline value in the Propofol group within 5 min after electroconvulsive therapy.

The percentage saturation of haemoglobin with oxygen was monitored throughout the procedure. Although at all times of observation and on most occasions percentage saturation of haemoglobin remained within clinically acceptable limits. The difference observed was not statistically significant at any time interval, indicating proper tissue oxygenation during procedure.

There was fall in respiratory rate in both the groups after ECT, however the difference observed was not statistically significant at any time interval. It reached the initial value in 5 minutes post ETC.

More complications were observed in Thiopentone sodium group as compared to Propofol group. In study conducted by Usha Daria, Vinod Kumar (in April 2012)<sup>13</sup>, common side effects observed with Thiopentone were delirium, laryngospasm, bronchospasm, where intubation was needed, headache, body ache, pyrexia, nausea, vomiting and thrombophlebitis. With Propofol headache, body ache and thrombophlebitis was observed in 3%, 4% and 3% of patients respectively. Authors concluded that Propofol is the drug of choice for modified ETC.

## CONCLUSION

An effort to avoid or minimize the physiologic sequelae and attendant complications of electroconvulsive therapy, a technique of modified electroconvulsive therapy has evolved gradually, featuring the use of drugs to minimize the detrimental effects of electroconvulsive therapy without the concomitant abolition of the essential beneficial effects.

Based on the present study, we conclude that Propofol when compared to Thiopentone sodium is a safe anesthetic agent for electroconvulsive therapy with minimal side effects.

Premedication with Glycopyrrolate prevented effects of parasympathetic stimulation occurring during ictal and post ictal phase. Propofol is superior to Thiopentone sodium in attenuating the physiological response to electroconvulsive therapy with milder hemodynamic change and better recovery profile.

## REFERENCES

1. John L. Beyer, M.D., Andrew D. Krystal Mehul V. Mankad Richard D. Weiner - Clinical Manual of ECT, first edition 2010 Chapters, introduction to ECT History of Electroconvulsive Therapy page - 3 to 8. Anaesthetics and other medications 81-96 ictal motor response 97-104, ictal encephalographic response, 105 - 128, Cardiovascular response 129- 138.
2. Fink M (1984): Meduna and the origins of convulsive therapy. *Am J Psychiatry* 141: 1034-1041.
3. George Y. Gaines and D. Ian Rees: Electroconvulsive therapy and anaesthetic considerations: International Anaesthesia Research society: *Anaesthesia Analogue*, 1345-56
4. Pearlman T, Loper M (1990) - should psychiatrists administer anaesthesia for ECT - *AMJ psychiatry* 147:1553-6
5. Manjula BP, Nagaraja PS (2015): Comparison of Thiopentone sodium and Propofol as anesthetic agents for modified electroconvulsive therapy. *Karnataka Anaesthesia Journal* 2015;1:128-33.
6. Boey WK, Lai FO. Comparison of propofol and thiopentone as anaesthetic agents for electroconvulsive therapy. *Anaesthesia* 1990;45:623-8.
7. Saito S, Kadoi Y, Nara T, Sudo M, Obata H, Morita T, et al. The comparative effects of propofol versus thiopental on middle cerebral artery blood flow velocity during electroconvulsive therapy. *Anesth Analg* 2000;91:1531-6.
8. Fredman B, d'Etienne J, Smith I, Husain MM, White PF. Anesthesia for electroconvulsive therapy: Effects of propofol and methohexital on seizure activity and recovery. *Anesth Analg* 1994;79:75-9.
9. Mulier JP, Wouters PF, Van Aken H, Vermaut G, Vandermeersch E. Cardiodynamic effects of propofol in comparison with thiopental: Assessment with a transesophageal echocardiographic approach. *Anesth Analg* 1991;72:28-35.
10. Gazdag G, Kocsis N, Tolna J, Iványi Z. Etomidate versus propofol for electroconvulsive therapy in patients with schizophrenia. *J ECT* 2004;20:225-9.
11. Rosa MA, Rosa MO, Belegarde IM, Bueno CR, Fregni F. Recovery after ECT: Comparison of propofol, etomidate and thiopental. *Rev Bras Psiquiatr* 2008;30:149-51.
12. Kadiyala PK, Kadiyala LD. Anaesthesia for electroconvulsive therapy: An overview with an update on its role in potentiating electroconvulsive therapy. *Indian J Anaesth* 2017;61:373-80.
13. Dr Usha Daria and Dr Vinod Kumar Comparison of thiopentone and Propofol- as Better Anaesthetic agent for Modified Electroconvulsive Therapy. *Asian Journal of Pharmaceutical and Clinical Research*; 2012; Vol.5, Suppl 2: 227-230.