Comparison of maintenance ECT versus Clozapine on psychopathology and regional cerebral blood flow in treatment-resistant schizophrenia: A randomized controlled trial

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Introduction

- In treatment-resistant schizophrenia (TRS), Clozapine is the only approved treatment but has many adverse effects.
- Up to one-third of the patients show resistance to Clozapine therapy, necessitating alternative treatment.
- Electroconvulsive Therapy (ECT) is a safe and effective treatment modality in schizophrenia, but acute treatment effects last for few weeks to months.
- There are no controlled studies regarding Maintenance-ECT (M-ECT) in TRS.
- The present study compared the efficacy and safety of M-ECT vs standard Clozapine therapy in TRS.
- The regional blood flow changes (SPECT-CT brain) with treatment were compared and correlated with the treatment effects.

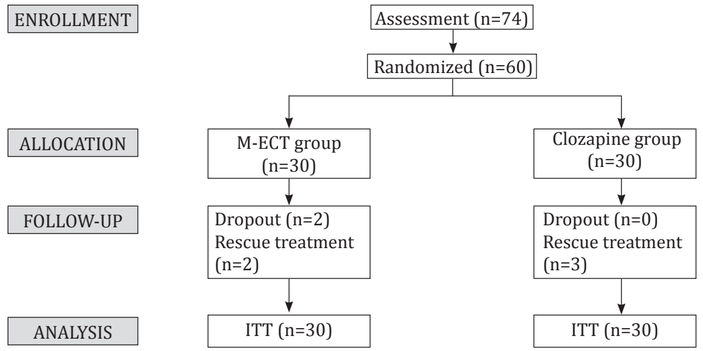
Methods

- **Study design:** Randomised, open-label, parallel-group clinical trial conducted in AIIMS, Bhubaneswar, over a time frame of 16 months [clinicaltrials.gov : NCT03807882]
- **Inclusion criteria:** Patients with TRS (TRRIP consensus criteria), aged 18–60 years, of either gender, with written informed consent from LAR were included.
- **Exclusion criteria:** Patient already on clozapine or ECT, or with psychoactive substance abuse, any co-morbid major medical condition, pregnant and breastfeeding females were excluded.
- **Randomisation:** Block Randomisation into two treatment arms, with a 1:1 allocation ratio.
- **Blinding:** The outcome assessors were kept blinded to the treatment allocation.
- The relevant socio-demographic and clinical data were collected in a structured case record form.
- **Outcome measures:**

  Primary:
  - Severity of symptom dimensions by PANSS

  Secondary:
  - Severity of the illness by CGI-SCH
  - Global assessment of functioning (GAF)
  - Cognitive deficits by MoCA
  - Regional cerebral perfusion changes by SPECT-CT brain
  - Number of patients requiring rescue treatment (Clozapine and fortnightly M-ECT) for non-responders
- **Intervention:**
  - **M-ECT Group:** Acute ECT (brief pulse, bilateral, six sessions over two weeks) followed by M-ECT weekly sessions for the first month, then biweekly for the next two months and then once every month for the following three months
  - **Clozapine Group:** Target dose of 250-400 mg per day in two divided doses as per tolerability (Maudsley guideline)
- PANSS, CGI–SCH, GAF, and MoCA were measured at baseline and re-administered after 6 weeks, 3 months and 6 months respectively, to compare the changes in the scores, within each group and between the groups.
- SPECT-CT brain was done using 99mTc-ethyl cystine dimer (ECD) at baseline and post-treatment at 6 months to evaluate the changes in regional cerebral perfusion with treatment
- **Statistical analysis:** Means of continuous variables were compared within the group using the paired t-test and between the groups using independent samples t-test. Missing values were handled using multiple imputations and intention-to-treat (ITT) analysis was performed for all outcome measures.
- **Sample size calculation:** Power= 90%, Effect size= 10 points in total PANSS scores, SD= 9.9, significance level p=0.05, Sample size: 30 in each group

Figures/Graphs



Results

At baseline, the study groups were homogenous with respect to the sociodemographic and clinical variables

Table 1: Improvement of different outcome parameters over time (after Intention-to-treat analysis)

Time of Assesment	Groups		P value	Groups		P value
	M-ECT (n=30)	Clozapine (n=30)		M-ECT (n=30)	Clozapine (n=30)	
	PANSS-P			**CGI-SCH-S**		
0-6 weeks	13.84 ± 1.18	6.28 ± 0.97	< 0.0001	2.31 ± 0.15	1.15 ± 0.12	< 0.0001
0- 12 weeks	18.72 ± 1.33	12.36 ± 1.18	< 0.0001	2.92 ± 0.17	2.07 ± 0.13	< 0.0001
0-24 weeks	21.13 ± 1.30	16.11 ± 1.27	0.005	3.07 ± 0.18	2.41 ± 0.17	0.004
	PANSS-N			**CGI-SCH-I**		
0-6 weeks	9.88 ± 0.99	5.07 ± 0.69	< 0.0001	2.42 ± 0.14	3.29 ± 0.11	< 0.0001
0- 12 weeks	14.02 ± 1.07	9.51 ± 0.82	0.001	2.14 ± 0.16	2.71 ± 0.13	0.005
0-24 weeks	16.17 ± 1.26	12.23 ± 1.14	0.021	2.11 ± 0.17	2.61 ± 0.15	0.021
	PANSS-G			**MoCA**		
0-6 weeks	22.63 ± 1.96	11.16 ± 1.48	< 0.0001	-1.06 ± 0.17	-0.87 ± 0.11	0.326
0- 12 weeks	30.62 ± 2.49	20.40 ± 1.74	0.001	-1.21 ± 0.18	-1.52 ± 0.14	0.196
0-24 weeks	34.62 ± 2.39	27.37 ± 1.95	0.018	-1.34 ± 0.24	-1.72 ± 0.18	0.217
	PANSS-T			**GAF**		
0-6 weeks	46.35 ± 3.78	22.51 ± 2.73	< 0.0001	-25.38 ± 2.46	-8.48 ± 1.79	< 0.0001
0- 12 weeks	63.36 ± 4.42	42.28 ± 3.41	< 0.0001	-36.12 ± 2.47	-22.99 ± 2.59	< 0.0001
0-24 weeks	71.93 ± 4.42	55.71 ± 3.87	0.005	-41.85 ± 2.34	-30.16 ± 3.02	0.002

Table 2: Comparison of the change in regional cerebral blood perfusion (SPECT CT brain) (from baseline to the end of 24 weeks) between the treatment groups

Variables	Groups		P value	Variables	Groups		P value
	M-ECT (n=30)	Clozapine (n=30)			M-ECT (n=30)	Clozapine (n=30)	
	Mean ± SEM	Mean ± SEM			Mean ± SEM	Mean ± SEM	
LLPFC	-0.025 ± 0.008	0.017 ± 0.009	0.001	RLPFC	-0.014 ± 0.004	0.002 ± 0.006	0.035
LMPFC	-0.019 ± 0.007	0.007 ± 0.006	0.007	RMPFC	-0.009 ± 0.005	0.016 ± 0.006	0.001
LLT	-0.011 ± 0.004	0.017 ± 0.005	< 0.001	RLT	-0.019 ± 0.006	0.005 ± 0.007	0.023
LMT	-0.022 ± 0.013	0.021 ± 0.015	0.047	RMT	-0.035 ± 0.008	-0.024 ± 0.010	0.375
LSP	-0.014 ± 0.010	-0.007 ± 0.008	0.547	RSP	-0.013 ± 0.008	0.005 ± 0.010	0.166
LIP	0.015 ± 0.009	0.006 ± 0.007	0.459	RIP	-0.001 ± 0.008	-0.004 ± 0.009	0.773

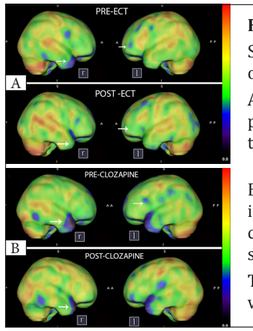


Fig:

SPECT-CT 3-D stereotactic surface projection (3D-SSP) maps of the brain of

A) A patient in the M-ECT group, showing significant improvement in perfusion in the left prefrontal cortex and right temporal cortex in post-treatment scan as compared to baseline scan.

B) A patient in the Clozapine group, showing improvement in perfusion in the left prefrontal cortex, partial improvement in the right temporal cortex and no improvement in the left temporal cortex in post-treatment scan compared to the baseline scan.

The greater improvement in perfusion with M-ECT over Clozapine is visually appreciable.

Conclusions

- M-ECT was superior to clozapine treatment over six months in reducing the positive and negative symptoms, general psychopathology, and the severity of illness, along with improving the global functionality in patients with TRS
- These findings were corroborated by significantly better blood perfusion with M-ECT over clozapine treatment in the prefrontal and temporal cortices
- Both M-ECT and clozapine produced comparable improvement in cognition
- Both interventions were comparable in terms of safety, without any serious adverse effect
- In TRS, clozapine is the first-line drug, but in view of our findings, we suggest that M-ECT can be a better option for such patients

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