ELECTROCONVULSIVE THERAPY (ECT) FOR THE MANAGEMENT OF NEUROLEPTIC MALIGNANT SYNDROME (NMS) IN ADULTS

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ABSTRACT

Objective: To determine the efficacy and safety of electroconvulsive therapy (ECT) for the management of neuroleptic malignant syndrome (NMS) in adults.

Study Design: Open label, unblinded series.

Place and Duration of Study: This study was carried out at the Department of Neurology, Military Hospital Rawalpindi, from Jan 2015 to Dec 2015.

Material and Methods: All the patients with the diagnosis of NMS during the study period were included in the study. Consective non-probability sampling technique was used. Patients were divided into two groups; uncomplicated and complicated cases of NMS.

Results: A total of nineteen patients were included in this pilot study. Out of all, thirteen (68.4%) were males and six (31.6%) were females. Mean age of the patients was 35.05 (SD 13.362) years. The drug classes causing NMS were antipsychotic medicines in 73.7% of patients and antiemetics in 26.3% of patients. Mean electroconvulsive therapy (ECT) sessions given were 6.16 (SD 2.062). Following treatment n=16 (84.2%) patients had complete recovery while n=3 (15.3%) patients died.

Conclusion: In this small, open label, unblinded study ECT appears effective and safe in treating NMS in adults. Larger randomized studies will help to confirm data emerging from this preliminary study.

Keywords: Electroconvulsive therapy, Hyperthermia, Neuroleptic malignant syndrome.

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a life threatening idiosyncratic reaction caused by an adverse reaction to medications with dopamine receptor - antagonist properties or the rapid withdrawal of dopaminergic medications and is characterized by fever, altered mental status, muscle rigidity and autonomic dysfunction. It is associated with virtually all neuroleptics, including newer atypical antipsychotics, as well as a variety of other medications that effect central dopaminergic neurotransmission e.g. antiemetic medications. The first reported case of NMS appeared in 1956, shortly after the introduction of the antipsychotic drug chlorpromazine. Additional case reports quickly followed, and in a 1960 study French clinicians gave the syndrome its current name when they reported on the adverse effects of the newly introduced neuroleptic haloperidol and characterized a "syndrome malin des neuroleptiques". Pooled data from 1966 to 1997 suggested the incidence of NMS ranges from 0.2% to 3.2% of psychiatric inpatients receiving neuroleptic. However, as physicians have become increasingly aware of the syndrome and as new neuroleptic agents have become available, the incidence has declined more recently to around 0.01% to 0.02%[1]. Patients develop NMS within hours or days after exposure to a causative drug, with most exhibiting symptoms within 2 weeks nearly all within 30 days[2]. The clinical course typically begins with muscle rigidity followed by a fever within several hours of onset and mental status changes that can range from mild drowsiness, agitation, or confusion to a severe delirium or coma. Signs of autonomic nervous system instability that frequently accompany NMS include labile blood pressure, tachycardia, sialorrhea, diaphoresis, flushing, skin pallor,

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and incontinence. Once symptoms appear, progression can be rapid and can reach peak intensity in as little as 3 days with muscle rigidity as the most frequently described motor sign NMS remains a critical consideration in the differential diagnosis of patients presenting with fever and mental status changes[3]. In our clinical practice since prompt recognition can prevent significant morbidity and death. Treatment includes immediately stopping the offending agent and implementing supportive measures, as well as pharmacological interventions. In severe cases where drug treatment remains ineffective and complications develop electroconvulsive therapy is given which is effective, safe and lifesaving.

PATIENTS AND METHODS

This open label unblinded pilot study was carried out at neurology department of Military Hospital, Rawalpindi from Jan 2015 to Dec 2015 for a total duration of one year. Nineteen patients with the diagnosis of neuroleptic malignant syndrome were included in the study. All the patients were managed in the intensive care unit (ICU) of the hospital. Permission from hospital ethical committee was obtained prior to start of the study. A written informed consent was also obtained from all the patients or the families wherever applicable. NMS was defined according to expert panel consensus as having most of it, if not all of following characteristics[4].

1. Exposure to dopamine antagonist, or dopamine agonist withdrawal, within past 72 hours.
2. Hyperthermia (>100.4 F or >38.0 C at least at 2 occasions, measured orally)
3. Rigidity
4. Mental status alternation (reduced or fluctuating level of consciousness)
5. Creatinine kinase elevation (at least 4 times the upper limit of normal).
6. Sympathetic nervous system lability, defined as at least 2 of the following: blood pressure elevation (systolic or diastolic ≥25 percent above baseline), blood pressure fluctuation (≥20 mmHg diastolic change or ≥ 25 mmHg systolic change within 24hours), diaphoresis, urinary incontinence.
7. Hyper metabolism, defined as heart-rate increase (≥ 25 percent above baseline) and respiratory rate increase (≥ 50 percent above baseline).
8. Negative work-up for infectious, toxic, metabolic or neurologic causes.

NMS was classified into three categories

a. Medical treatment resistant NMS

Patients who did not respond to 7 days of pharmacological therapy

b. Complicated NMS

Patients in which one of the known following complications developed during course of treatment.

1. Aspiration pneumonia
2. Respiratory failure requiring ventilator support
3. Rhabdomyolysis
4. Renal failure
5. Disseminated intravascular coagulation
6. Deep vein thrombosis
7. Seizures
8. Cardiovascular arrhythmia and collapse

c. Severe NMS

Patients with severe rigidity; catatonia or coma; temperature ≥40°C (104 °F); heart rate ≥120 bpm with severe autonomic dysfunction were classified as having severe NMS.

All patients were given pharmacological therapy with dopamine agonists. Amantadine in dose of 200mg daily in two divided doses and bromocriptine in escalating doses ranging from 2.5mg up to 40 mg daily in three divided doses. Electroconvulsive therapy was given to medical refractory, complicated and severe NMS patients. ECT was administered by a team including psychiatrist, neurophysician, anesthesiologist and nurses. The patients were made Nil Per Oral

(NPO) and an informed consent was taken. The gold standard bilateral electrode placement technique was used. A brief pulse (0.5 to 2.0 milliseconds) was used as stimulus. The patents were preoxygenated. Premedication with atropine (0.4mg) was administered to prevent vagally-mediated bradycardia and excess oral and respiratory secretions. Propofol was used as anesthetic agent and muscle relaxants were used as per the need. Response to treatment outcome and side effects of ECT were also studied. Data for each patient was entered on a patient's proforma by the researchers. Data was analyzed using Statistical Package of Social Sciences SPSS version 17. Descriptive statistics were calculated for both qualitative and quantitative variables. Frequencies and percentages were calculated for qualitative variables like gender, causative drug, types of NMS and outcomes of patients. Means and standard deviations were calculated for quantitative variables like age, days to NMS development, serum creatinine kinase levels, days of medical treatment and electroconvulsive therapy sessions.

RESULTS

A total of nineteen (n=19) patients were included in this study. Out of them thirteen (68.4%) were males and six (31.6%) were females. Mean age was 35.05 yrs, (SD 13.362). Causative drug of NMS in our study population was antipsychotic in 73.7% of patients and antiemetic in 26.3% of patients (table-I).

Different classes of NMS in our study population were as given in the table-II.

The mean days of medical treatment were 3.53 (SD 1.962) before start of ECT and the mean ECT sessions given were 6.16 (SD 2.062). Total mortality was n=3 (15.8%). ECT was safe as none of the patients developed any significant side effects. Among the patients who died, even with ECT, Two (n=2, 10.5%) were suffering from complicated NMS while one (n=1, 5.2%) had severe NMS (table-III).

Table-I: Drugs causing neuroleptic malignant syndrome (NMS).

Causative agent	Frequency (n)	Percentage (%)
Antipsychotic	14	73.7
Antiemetic	5	26.3
Total	19	100.0

Table-II: Different categories of NMS found in this study.

Types of NMS	Frequency	Percentage (%)
Medical treatment refractory NMS	3	15.8
Complicated NMS	11	57.9
Severe NMS	5	26.3

Table-III: Outcome of NMS cases following combination of medical therapy and Electroconvulsive Therapy (ECT).

Outcome of patients	Frequency	Gender		Percentage (%)
		Male	Female	
Recovered	16	11	5	84.2
Died	3	2	1	15.8

DISCUSSION

NMS is a self-limiting disease once the causative agent is discontinued with an average duration of recovery in the range of 7 to 15 days. Successful treatment of NMS depends on early clinical recognition and prompt institution of aggressive supportive care as severe complications are common during course of disease which sometimes prove to be fatal with an estimated mortality between 10 and 20 percent[5]. In our study mortality was 15.8% and

all the three patients who died developed respiratory failure requiring ventilator support. Almost sixty percent of our patients developed complicated NMS which further emphasizes the importance of early intensive supportive care.

Recommendations for specific medical treatments in NMS are based upon case reports and clinical experience, not upon data from clinical trials. Their efficacy is unclear and disputed yet they are frequently used because of anecdotal evidence of efficacy, lack of other proven treatment and high morbidity and mortality of the disorder[6]. We used bromocriptine and amantadine as dantrolene is not available in Pakistan. The use of any of these medications is controversial and largely unsupported[7]. A retrospective analysis of published cases indicated that the use of bromocriptine and/or dantrolene appeared to hasten clinical response. Time to complete recovery was reduced from a mean of 15 days (with supportive care alone) to nine days (with dantrolene) and 10 days with (with bromocriptine). Another analysis found reduced mortality: 8.6 percent in patients treated with dantrolene, 7.8 percent in patients treated with bromocriptine, and 5.9 percent in patients treated with amantadine compared with 21 percent in those receiving supportive care alone[8,9].

Usually the effects of pharmacotherapy are thought to appear within the first few days, and if they do not, the drug is not likely to be effective. We observed that 15.8% of our patients were refractory to medical treatment as they did not have substantial response to seven days of medical therapy. In resource poor settings these patients may not have access to intensive care treatment allowing complications to set in very early. It is at this stage the role of ECT comes in, for it appears to be effective in not only severe but also in refractory and complicated cases, with a marked reduction in mortality. In another review of published cases we found a lower mortality rate in ECT treated patients compared with those receiving supportive care alone (10.3 versus 21 percent)[10]. We used ECT as a first line therapy in severe NMS patients (26.3%) and second line therapy in medically resistant and complicated NMS patients and found that ECT is not only safe but very effective as 84.2% of our patients benefitted with full recovery. Scheftner and shulman[11] in their case series proposed ECT as an effective treatment modality when drugs are not effective. Their literature review indicates that response to treatment is usually apparent after a few sessions which in our study was 6.16 sessions. Our study also confirms the observation of Trollor et al[12]. who reviewed 46 cases in the literature and 9 patients of their own, in 31 cases (56%), ECT was used after pharmacotherapy had failed, while in 40 cases (73%), it was the first line treatment. Full recovery was seen in 25 cases (63%) and partial recovery in 11 cases (26%), with a total of 36 patients (90%) benefiting from the treatment.

There are safety concerns for ECT in NMS in literature review. Cardiovascular complications like ventricular fibrillation and cardiac arrest with permanent anoxic brain injury have been reported. Other authors also report uncontrolled spontaneous seizures and aspiration pneumonia complicating ECT treatment for NMS[13]. We found ECT to be very safe as none of our patients developed any complications, three patient who died succumbed to severe complications of disease.

CONCLUSION

In this small, open label, unblinded study ECT appears effective and safe in treating NMS in adults. Larger randomized studies will help to confirm data emerging from this preliminary study.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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