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Role of Therapeutic Plasma Exchange in the Treatment of Myasthenia Gravis: A Tertiary Hospital - Based Observational Study

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Abstract: ***This study aimed to analyze the experience related to the indication, complication, and outcome of Therapeutic Plasma Exchange (TPE) in Myasthenia gravis (MG). Plasma exchange is the therapeutic modality established in MG with a positive recommendation based on a strong consensus of class 3 evidence. A total of 15 patients of MG were submitted to a total of 17 cycles and 65 sessions of TPE. It was performed using a single volume plasma exchange with intermittent cell separator (Hemonetics) by Femoral or central line access and scheduled preferably on alternate day intervals. The immediate outcome was assessed shortly after each session and the overall outcome at discharge. A total of 26 patients of MG were admitted to our hospital during the study period of two years.15 (57.69%) patients had TPE performed with a mean age of 32 years (M: F = 3: 1). The mean number of TPE sessions was 4.2 (SD±1.2), volume exchange was 2215 ml (SD±435), the overall incidence of adverse reaction was 21.7%. All patients had immediate benefits from each TPE cycle. Good acceptance of the procedure was observed in 78.3% of patients. TPE may be considered as one of the treatment options, especially in developing countries like ours, as it is relatively less costly but as effective for myasthenic crisis as other modalities.***

Keywords: Adverse reaction, myasthenia gravis, therapeutic plasma exchange

1. Introduction

Therapeutic apheresis encompasses a variety of blood processing techniques, which improve the outcome of susceptible clinical disorders. These techniques include, in part, therapeutic plasma exchange (TPE), therapeutic cytoreduction, in - line cellular immunomodulation, and plasma treatment. Some of these applications are the primary therapy for certain disease processes, and many others are considered secondary or adjunctive therapy. Still, both categories of apheresis treatments are effective and beneficial [1].

Myasthenia gravis (MG) is a well - known autoimmune disease characterized by antibodies against postsynaptic nicotinic acetylcholine receptors and fluctuating weakness, sometimes life - threatening. MG has an annual incidence of approximately 30 new cases per million, approximately 15–20% of these patients will go into myasthenia gravis crisis (MGC), and 3–8% of all patients who go into MGC will die from this condition [2]. TPE is a therapeutic modality established in MG with a positive recommendation based on a strong consensus of class III evidence and in category I of American society for apheresis [3, 4, 5]. The two most common indications for acute exchange are myasthenic crisis and myasthenia exacerbation [4]. There is no adequate randomized control trial, but many cases report short - term benefits from plasma exchange in MG, especially in MGC [6].

Therapeutic plasma exchange is an extracorporeal blood purification technique. The plasma is separated from the blood, discarded in total, and replaced with a substitution fluid such as albumin or plasma collected from healthy donors. This is generally performed to remove high - molecular - weight substances such as pathogenic autoantibodies, immune complexes, cryoglobulins, and toxins accumulated in the plasma [7]. Its efficiency in MG is due to removing proteins of autoimmune biological activity, mainly antibodies to the acetylcholine receptor, leading to short - term improvement of neuromuscular junction transmission, muscular strength, and motor performance [8]. Rapidly reducing the autoantibodies may sometimes lead to a rebound overproduction of the same antibodies. This rebound production of antibodies is thought to make the replicating pathogenic cells more vulnerable to cytotoxic drugs. For this reason, it is often performed to enhance the effectiveness of cytotoxic drugs. Usually, TPE is combined with immunosuppressive treatments, such as intravenous immunoglobulin (IVIG), prednisone, and azathioprine, to avoid rebound effects and maintain improvement [9]. Both IVIG and TPE are effective disease - stabilizing therapies for patients with MGC [10]. To date, neither IVIG nor TPE has established clear clinical dominance over the other for the treatment of MGC. As the societal cost of health care has increased, it is imperative to optimize patient care and identify areas where costs can be reduced. Although the cost should never be the primary reason for selecting a therapy, it is reasonable to consider this aspect in cases where one beneficial therapy is not superior to another [11, 12]. Compared to IVIG, plasma exchange is considered equally effective and is a comparatively cheaper mode of immunomodulatory treatment for myasthenia crisis.

We analyzed experience related to the indications, complications, and outcome of TPE in the treatment of MG patients, and several aspects of the procedure itself were also reviewed.

2. Methods

2.1. Study design

Patients of MG and MGC admitted to the Neurology Intensive Care Unit (ICU) and on mechanical ventilation during the period January 2016 to December 2018 (2 years study) were included in the study TPE (average cost is 35, 000tk /cycle) was initiated and monitored by the Department of Transfusion Medicine, BSMMU, Dhaka, Bangladesh.

2.2. Study subject description

From January 2016 to December 2018, there were total. Twenty - six patients of MG were admitted to BSMMU.15 (57.6%) of them received TPE. We reviewed TPE protocols of these consecutive series of 15 patients of MG in ICU/HDU. They were submitted to a total of 17 cycles and 65 sessions of TPE during this period. Clinical diagnosis of MG was complemented by laboratory exams, such as repetitive nerve stimulation tests, anti - acetylcholine receptor (Anti AChR) antibodies. Patients were classified according to the Myasthenia Gravis Foundation of America (MGFA) scales expressing the clinical deficit before TPE. Gender, age - onset of MG, level of serum Anti AChR binding antibodies.

The patient's blood counts, electrolytes, serum proteins, coagulation profile, and vitals were checked, and appropriate steps were taken to correct the deranged parameters. The consent for the procedure was taken from the patient/patient's relatives before the procedure. TPE was performed using a single volume plasma exchange with intermittent cell separator (Hemonetics MCS plus) machines by femoral or central line access using 12 French double lumen dialysis catheters. It was scheduled preferably on alternate - day intervals for 8–10 days. Anticoagulation with citrate (ACD) was systematically used. Replacement of plasma removed during the session was done with isotonic sterile saline to make up one - half of the volume and with 5% purified human albumin and fresh frozen plasma to complete it. Careful monitoring of hemodynamic parameters was done, and complications during or following TPE were rapidly recognized and reverted by rationale interventions of medical staff that assisted the procedure. Indications for TPE, number of cycles and sessions, duration of each session, the volume of plasma exchanged, and patient tolerance to the procedure were systematically recorded. Calcium replacement with 10 ml of 10% calcium gluconate was infused over 15 min approximately halfway through the procedure to avoid citrate toxicity. Complete blood count, serum electrolytes, and albumin were monitored daily. The immediate outcome was assessed shortly after each session, and the overall outcome was assessed at the time of discharge. The amount of plasma to be exchanged must be determined to the estimated plasma volume (EPV). Using the formula, a simple means of estimating the EPV can be calculated from the patient's weight and hematocrit. EPV = (0.65 × wt [kg]) × (1 − Hcv) [13].

3. Results

A total of 15 (57.6%) patients of MG or MGC, out of which nine were on mechanical ventilation, received plasma exchange during the period of 2 years from January 2016 to December 2018. A total of 17 cycles and 65 sessions of TPE were done. It included four females and 11 males with age groups ranging from 18 to 62 years. The mean age of onset was 32 years. Using MGFA clinical classification, cases were classified as class IV a (6 cases), class IV b (6 cases), and class V (3 cases). All patients responded transiently favorable to each cycle of TPE, but none had been exclusively under this therapy. TPE was indicated due to myasthenic crisis in 9 with severe motor dysfunction, especially related to bulbar palsy, and the rest six were offered TPE as there was a progressive worsening of myasthenic symptoms despite optimal treatment. The mean number of TPE sessions was 4.2 (standard deviation [SD] ±1.2). The mean volume of plasma exchanged was 2215 ml (SD ± 435), and the mean time duration of each session was 207 min (SD ± 25). Side effects were mild such as citrate toxicity in 12, hypotension in 2, catheter - related problems in 1. No infection was observed, and no death occurred as a consequence of TPE. Good TPE acceptance occurred in 74.2% of cases.

Each session of TPE resulted in immediate improvement of clinical status in every patient. Death was registered in three patients, but it was not directly related to TPE.

4. Discussion

Myasthenia gravis was the second most common indication for TPE in 1997 and was first described as a form of treatment for MG in 1976 by Pinching and Peter. They performed plasma exchange in 3 patients and found partial improvement in muscle weakness and fatigue, suggesting that a humoral factor in the plasma was causing the disorder of neuromuscular transmission [14]. A close correlation with clinical, functional improvement and a reduction in acetylcholine receptor antibody levels was found. There were a few randomized control trials in MG; a trial of 87 patients showed the same efficacy after two weeks of TPE for the treatment of MG exacerbation compared to IVIG [15]. Gajdos et al., in their meta - analysis on TPE in MG, concluded that TPE provides short - term benefits in patients with MG especially myasthenic crisis. [6]. A multicenter study from Taiwan showed that 34.9% of TPE was indicated for MG patients [16].

In our study, male: female 3: 1 (about) TPE was indicated due to myasthenic crisis in 9 (60%) patients and progressive worsening despite treatment in 1 (6.6%). Similarly, Carandina - Maffeis et al. performed plasma exchange in 7 (26.9%) patients with myasthenic crisis [17]. Werneck et al. used plasma exchange as a specific treatment modality in 24 (16.6%) patients with worsening myasthenic symptoms [18].

TPE was indicated in patients having a severe motor deficit, especially bulbar dysfunction, or due to worsening of deficit

induced by immunosuppressive as it is a drug of the first choice in the therapy of MG. TPE was repeated in four cases because other therapies failed to achieve sustained motor performance for daily life activities. Case no 12 had three cycles in a monthly schedule of four consecutive alternate day sessions. Cases no 5, 24, and 31 had two cycles in a two - month schedule of five consecutive alternate day sessions of TPE, respectively. It was observed that chronic TPE is an effective therapy in generalized MG refractory to other treatments. Rodnitzky and Bosch described two cases of intermittent plasma exchange (PE) therapy prescribed up to 5 years without significant side effects [19].

The perception that TPE is a benign procedure has undoubtedly contributed to its widespread use for unproven indications. The overall incidence of adverse reaction reported in the literature range from 1.6% to 25%, with severe reaction occurring in 0.5– 3.1%, [20]. but in our study overall incidence of adverse reactions was 21.7%. The most common frequent complications were related to either vascular access or the composition of replacement fluids. Hematomas, infections, catheter blockage, and pneumothorax are the most frequent complication of vascular access, complicating 0.02–4%, citrate toxicity approximately 1.5–9%, hypotension or vasovagal reaction occurs in roughly 0.4–4% of procedures due to preexisting hemodynamic instability and anaphylactoid reactions to FFP are common and have been reported to occur with an incidence of up to 21% [21, 22]. In our study, we encountered catheter blockage in eight procedures (4.6%), but a culture of catheter tips was all negative, citrate toxicity occurred in twelve (6.8%), hypotension in two (1.14%), was reversed by fluid replacement and anaphylactic reaction occurred in 16 (9.14%) and was managed with intravenous hydrocortisone and diphenhydramine. Korach et al. observed that anticoagulant citrate dextrose solution complications were responsible for 3% of side effects in all procedures, like perioral tingling, trembling, dizziness, and hypotension [23]. Seggia et al. also presented a list of side effects in their patients who were all easily managed, such as 10.4% of paresthesias, 2% of hypotension, and 10.4% of allergic reactions [24]. Three patients were in a chronic ventilator - dependent state with diaphragmatic paralysis. They had prolonged hospitalization, evolving to death from sepsis that occurred 3 and 4 months after TPE, but no direct relationship could be established. Kirov et al. found a mortality rate of 0.006% from two large mobile apheresis services, and the mortality rate was 0.2% in a survey of 7 years in Mexico [21, 25, 26]

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