CASE REPORT

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Type-I hypersensitivity reactions in crisis myasthenic gravis patients after Therapeutic Plasma Exchange (TPE): a case report

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ABSTRACT

Background: Therapeutic Plasma Exchange (TPE) is one of the acute management procedure for patients with Myasthenia Gravis (MG) crisis where the side effects after the procedure are quite minimal. This case report discusses a type-I hypersensitivity reaction that occurred after TPE in a patient with Myasthenia Gravis (MG) crisis.

Case Presentation: A 56-year-old woman with myasthenia gravis (MGFA grade V) was admitted with respiratory distress and diagnosed with a myasthenic crisis. Therapeutic Plasma Exchange (TPE) with albumin was initiated to manage her crisis, but following the first TPE session, she developed a type-I hypersensitivity reaction, presenting as widespread urticaria. Despite antihistamine treatment, she experienced oxygen desaturation. Laboratory tests revealed elevated CRP, hypoalbuminemia, and electrolyte imbalances, likely exacerbated by pneumonia as a precipitating factor. TPE sessions continued under close monitoring, and her symptoms gradually stabilized.

Conclusion: This case highlights the importance of recognizing type-I hypersensitivity as a potential complication of TPE in MG patients. While TPE is effective in controlling myasthenic crises, prompt management of hypersensitivity reactions is crucial to prevent severe outcomes.

Keywords: Myasthenic Crisis, Therapeutic Plasma Exchange, Type I Hypersensitivity, Urticaria.
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INTRODUCTION

Myasthenia gravis (MG) is an autoimmune neurological disorder affecting the neuromuscular junction, characterized by fluctuating skeletal muscle weakness. The global incidence of MG ranges from 1.7 to 21.3 per million people. Despite available treatments, MG poses significant morbidity and mortality due to variable clinical symptoms, including ocular, bulbar, limb, and respiratory muscle weakness. This weakness is caused by autoantibodies that attack postsynaptic membrane proteins in the neuromuscular junction, leading to symptoms like ptosis, diplopia, facial changes, dysphagia, speech difficulties, respiratory distress, and progressive limb weakness.[1,2]

Myasthenia gravis (MG) exemplifies an antibody-mediated autoimmune disease and a type II hypersensitivity reaction, with most patients having autoantibodies against acetylcholine receptors, muscle-specific kinase (MuSK), or Lrp4.[1,3] Mortality in MG has declined to 2.2% annually due to treatments like acetylcholinesterase inhibitors, immunosuppressants, intravenous immunoglobulins, respiratory support, and Therapeutic Plasma Exchange (TPE).[4] TPE is particularly critical in acute myasthenic crises to prevent respiratory failure and death by removing autoantibody-rich plasma and replacing it with plasma or albumin.[5,6] Studies, including a meta-analysis by Ipe et al., show TPE's effectiveness in reducing disease severity in acute MG cases. However, TPE can lead to side effects, such as cardiovascular issues, sepsis, renal failure, and anaphylaxis, with a higher incidence of adverse effects compared to intravenous immunoglobulin (9.45% vs. 1.18%, $p < 0.0001$).[4,7]

Based on those mentioned above, this study aims to discuss a patient with a myasthenic crisis who developed a type I hypersensitivity reaction post-TPE, focusing on the evaluation of relevant laboratory parameters.

CASE PRESENTATION

A 56-year-old woman presented to the Emergency Department of Prof. Dr. dr. I.G.N.G Ngoerah Hospital with complaints of shortness of breath, which began that morning and worsened an hour before arrival. Her breathing was rapid and shallow. The previous day, she had started experiencing a productive cough and low-grade fever, despite taking medication.

Upon examination, the patient was alert, able to respond appropriately, but had difficulty speaking due to shortness of breath. She also reported double vision when looking left and right, along with decreased appetite. She denied symptoms like drooping eyelids, swallowing difficulties, abdominal pain, or bowel/urinary issues. She had a known history

of myasthenia gravis, regularly attended follow-ups, and had recently visited her clinic a week prior without complaints.

On her first hospital day, she experienced a single tonic-clonic seizure. Due to worsening respiratory distress, she was intubated on day two. By day four, she exhibited eye muscle weakness and more pronounced lower limb weakness, leading to the initiation of Therapeutic Plasma Exchange (TPE). Following the first TPE session, she developed hives and oxygen desaturation, which improved with diphenhydramine treatment. The second and third TPE sessions were completed on December 16th and 18th, with subsequent improvements in lower limb strength and spontaneous breathing.

By day 13, the patient could breathe and swallow well, and she was discharged. The patient was diagnosed with myasthenia gravis since 2010, she had previous intensive care admissions in 2010 and May 2023, including TPE and tracheostomy. She denied a history of other systemic illnesses, substance use, or family history of myasthenia gravis. Her daily medications included pyridostigmine, cyanocobalamin, methylprednisolone, and paracetamol. She is a homemaker caring for her grandchildren.

The patient appeared moderately ill with a Glasgow Coma Scale (GCS) score of E4V5M6. The Vital signs showed a blood pressure of 180/110 mmHg, a heart rate of 112 beats per minute, a respiratory rate of 28 breaths per minute, and a temperature of 37.5°C. Oxygen saturation was initially 88% on room air, which improved to 98% with a non-rebreather mask (NRM) at 12 liters per minute and stabilized at 95% with high-flow nasal cannula (HFNC). The patient's height and weight were recorded as 162 cm and 45 kg, respectively.

Based on the head examination, there were no signs of anemia or jaundice, and the pupils were reactive to light bilaterally at 3 mm. The neck examination showed no lymphadenopathy or stiffness. A cardiovascular examination revealed regular heart sounds (S1-S2) with no murmurs.

Vesicular breath sounds were present bilaterally in the respiratory examination, with no rhonchi or wheezing. Abdominal examination showed mild distension upon inspection, normal bowel sounds on auscultation, and no abnormalities in the liver or spleen upon palpation.

Extremities were warm with no leg edema, and muscle strength was assessed at 5/5 in the upper limbs and 4+/5 in the lower limbs. A distinct urticarial rash was noted on all four limbs (Figure 1). Neurologically, the patient showed no meningeal signs, and the Wartenberg test was negative. The counting test was limited, with the patient stopping at 3. The Myasthenia Gravis Composite Score was recorded at 20. Additionally, the patient experienced a generalized tonic-clonic motor seizure. The patient's hematology results were within normal limits (Table 1). Hemostasis function tests revealed a normal APTT, but low PT and INR levels in the patient (Table 2). Clinical chemistry results showed elevated CRP and fibrinogen levels, along with low levels of albumin, BUN, and fibrinogen (Table 3).

Blood gas analysis results revealed a mixed acid-base disorder, specifically mixed metabolic alkalosis and respiratory acidosis (Table 4). Electrolyte analysis showed hypokalemia, hyponatremia, and hypocalcemia (Table 5).

The impression obtained shows no abnormalities in the heart, suspected pneumonia, and thoracic spondylosis (Figure 2).

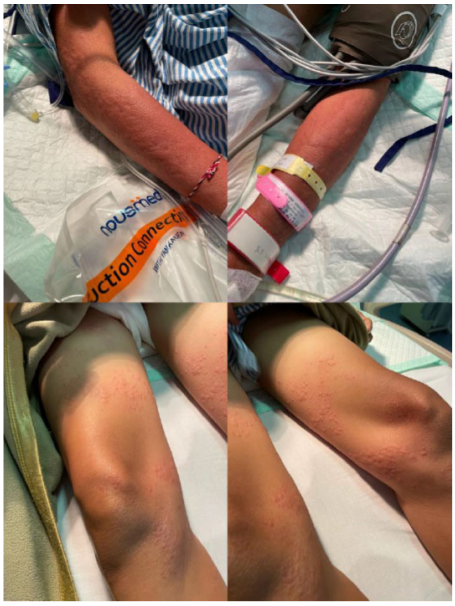

Figure 1. Clinical presentation of urticaria on all four extremities following TPE administration with Plasmanate albumin.

Table 1. Complete Blood Count Results at Prof. I.G.N.G Ngoerah Hospital

Variables	11/12/23	References
WBC (10^3/µL)	9.09	4.1-11.0
%Ne	67.50	47.0-80.0
%Ly	25.00	13.0-40.0
%Mo	7.20	2.0-11.0
%Eo	0.10	0.0-5.0
%Ba	0.20	0.0-2.0
#Ne (10^3/µL)	6.14	2.5-7.5
#Ly (10^3/µL)	2.27	1.0-4.0
#Mo (10^3/µL)	0.65	0.1-1.2
#Eo (10^3/µL)	0.01	0.0-0.5
#Ba (10^3/µL)	0.02	0.0-0.1
RBC (10^6/µL)	4.98	4.0-5.2
HGB (g/dL)	13.60	12.0-16.0
HCT (%)	41.00	36.0-46.0
MCV (fL)	82.30	80.0-150.0
MCH (pg)	27.30	26.0-34.0
MCHC (g/dL)	33.20	31-36
RDW (%)	13.80	11.6-14.8
PLT (10^3/µL)	165.00	140-440
NLR	2.70	≤3.13

WBC: White Blood Cells; Ne: Neutrophils; Ly: Lymphocytes; Mo: Monocytes; Eo: Eosinophils; Ba: Basophils; RBC: Red Blood Cells; HGB: Hemoglobin; HCT: Hematocrit; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; RDW: Red Cell Distribution Width; PLT: Platelet; NLR: Neutrophils to Lymphocyte Ratio

The chest CT scan revealed no visible masses in the lungs or mediastinum. Findings included pneumonia and fibrosis in the posterobasal and anterobasal segments of the right lower lung lobe, likely from an old inflammatory process. Multiple lymphadenopathies were observed in the aortocaval and subcarinal regions. Additionally, there was evidence of thoracolumbar spondylosis.

Based on those explanations above, the patient has been diagnosed with myasthenia gravis, classified as MGFA grade V. She also presented with urticaria attributed to a Type I hypersensitivity reaction following the administration of therapeutic plasma exchange (TPE). Additionally, the patient is under observation for a generalized tonic-clonic motor seizure, suspected to be an acute symptomatic seizure, with a differential diagnosis of symptomatic epilepsy.

The patient's treatment plan includes an IV infusion of 0.9% NaCl at a rate of 20 drops per minute. Methylprednisolone 250 mg is administered intravenously every 12 hours, along with oral pyridostigmine (Mestinon) 60 mg every 6 hours and intravenous levofloxacin 750 mg every 24 hours. A KCl drip of 50 mEq in 0.9% NaCl (500 cc) is provided, and plasmapheresis is conducted at a dose of 200-250 ml/kg body weight, divided across 5 sessions. In case of seizures, a slow intravenous bolus of diazepam 10 mg will be administered at a rate of less than 10 mg/min. Additionally, diphenhydramine 10 mg is given intravenously, and cetirizine 10 mg orally every 12 hours. Sucralfate 15 ml is also administered orally every 8 hours. The patient has been intubated, and oral hygiene is maintained with chlorhexidine every 12 hours and sterile water every 3 hours, with periodic suctioning as needed.

Table 2. Hemostasis Function Test Results at Prof. I.G.N.G Ngoerah Hospital

Variables	11/12/23	References
PT (seconds)	10.0	10.8-14.4
INR	0.86	0.9-1.1
APTT (seconds)	25.70	24-36

PT: Prothrombin Time; INR; International Normalized Ratio; APTT: Activated Partial Thromboplastin Time

Table 3. Clinical Chemistry Test Results at Prof. I.G.N.G Ngoerah Hospital

Variables	11/12/23	13/12/23	15/12/23	References
AST/SGOT (U/L)	28	-	-	<34
ALT/SGPT (U/L)	9	-	-	<55
CRP (mg/L)	29.50	-	-	<5
Albumin (g/dL)	-	3.20	-	3.4-4.8
Random Blood Glucose (mg/dL)	84	-	-	70-140
BUN (mg/dL)	5.80	-	-	7.0-18.7
Creatinine (md/dL)	0.67	-	-	0.57-1.11
e-GFR	98.26	-	-	≥90
Fibrinogen (mg/dL)	-	379.00	62.00	163-357

AST: Aspartate Aminotransferase; SGOT: Serum Glutamic-Oxaloacetic Transaminase; ALT: Alanine Aminotransferase; SGPT: Serum Glutamic-Pyruvic Transaminase; BUN: Blood Urea Nitrogen; e-GFR: Estimated Glomerular Filtration Rate

DISCUSSION

Myasthenia gravis is an autoimmune disease that affects neuromuscular transmission, causing localized or generalized muscle weakness characterized by fatigue.[3,8] Around 15-20% of myasthenia gravis patients will experience at least one myasthenic crisis. Myasthenic crisis is the most common complication of myasthenia gravis, involving worsening muscle weakness that can lead to respiratory failure, requiring intubation or mechanical ventilation. The median time for a myasthenic crisis to occur from the initial diagnosis is 8-12 months, though it can also be the initial

Table 4. Blood Gas Analysis Results at Prof. I.G.N.G Ngoerah Hospital

Variables	11/12	11/12	11/12	12/12	12/12	20/12	References
SO2c (%)	99.0	100.0	95.0	98.0	100.0	99.0	95-100
TCO2 (mmol/L)	36.20	35.30	31.90	33.90	-	35.60	24.00-30.00
pH	7.39	7.42	7.40	7.41	7.47	7.45	7.35-7.45
pCO2 (mmHg)	57.0	52.0	49.0	51.0	37.0	49.0	35.00-45.00
pO2 (mmHg)	151.00	165.00	77.00	97.00	182.00	115.00	80.00-100.00
BEecf (mmol/L)	9.5	9.2	5.6	7.7	3.2	10.1	-2 – 2
HCO3- (mmol/L)	34.50	33.70	30.40	32.30	26.90	34.10	22.00-26.00

SO2c: Calculated Oxygen Saturation; TCO2: Total Carbon Dioxide; pCO2: Partial Pressure of Carbon Dioxide; pO2: Partial Pressure of Oxygen; BEecf: Base Excess in the Extracellular Fluid; HCO3-: Bicarbonate Ion

Table 5. Electrolyte Test Results at Prof. I.G.N.G Ngoerah Hospital

Variables	11/12	12/12	12/12	13/12	15/12	17/12	18/12	19/12	20/12	References
Potassium (K)-Serum (mmol/L)	2.69	3.30	4.00	-	3.34	2.95	3.55	3.34	3.10	3.50-5.10
Sodium (Na)-Serum (mmol/L)	136	133	137	-	141	144	-	141	137	136-145
Chloride (Cl)-Serum (mmol/L)	99.4	-	-	-	103.0	107.6	-	102.8	-	94-110
Calcium (Ca) (mg/dL)	8.40	-	-	8.20	8.50	8.0	-	8.1	-	8.40-9.70
Magnesium (Mg) (mg/dL)	-	-	-	2.04	-	-	-	2.10	-	1.6-2.6

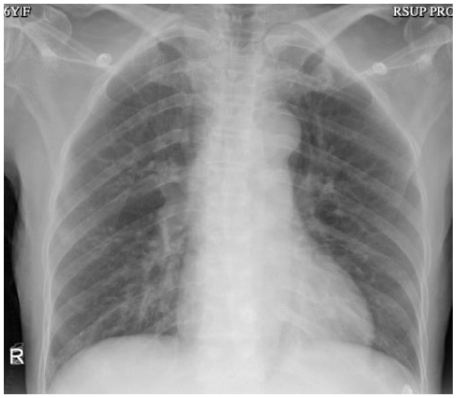

Figure 2. Patient's Chest X-Ray Results.

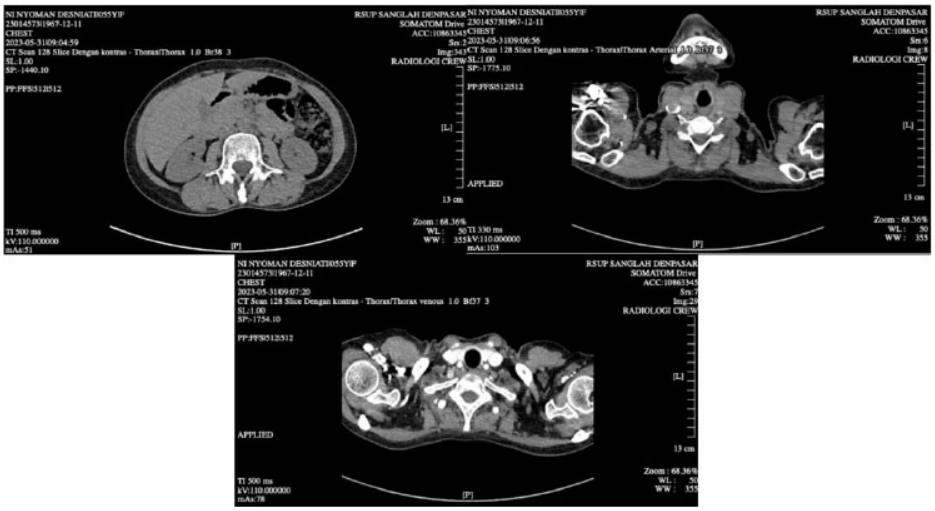

Figure 3. Patient's Chest CT Scan Results.

symptom in about one-fifth of patients. Generally, myasthenia gravis is twice as common in women as in men, with the peak age for women being 55 years, while the average age for myasthenic crisis onset is 59 years.[9,10] In this case, a 56-year-old woman with a 13-year history of myasthenia gravis experienced a myasthenic crisis.

Myasthenic crisis often involve upper respiratory muscles, respiratory muscles, or both, with inspiratory and expiratory muscle involvement leading to dyspnea, as seen in this case. Several factors can precipitate a myasthenic crisis, with infection being the most common. Studies report that 38% of myasthenic crisis cases are triggered by infections, such as bacterial pneumonia or viral upper respiratory infections. Other precipitating factors include aspiration pneumonia, surgery, pregnancy, certain medications, and tapering off immunomodulatory drugs. Additional triggers may include exposure to extreme temperatures, pain, sleep deprivation, and physical or emotional stress.[1,10] In this case, the myasthenic crisis was triggered by community-acquired pneumonia, as evidenced by the patient's initial cough, subsequent dyspnea, and chest X-ray findings. A thoracic CT scan was also performed to rule out tumors or masses, and no thymoma or other masses were found.

According to the Medical Scientific Advisory Board (MSAB) of the Myasthenia Gravis Foundation of America (MGFA), myasthenia gravis is classified into five grades, from Grade I (ocular muscle weakness only) to Grade V (intubation, with or without mechanical ventilation).[2] This case was classified as MGFA Grade V due to worsening respiratory muscle weakness requiring intensive care and intubation.

Laboratory tests to detect autoantibodies, such as AChR, MuSK, and LRP-4, are essential for diagnosing myasthenia gravis.[1,2] In this patient, myasthenia gravis was diagnosed 13 years ago, and she now presents with a myasthenic crisis marked by dyspnea, ocular and limb muscle weakness. Laboratory tests, including complete blood counts, were within normal limits, while hemostasis function tests showed normal APTT but low PT and INR. Clinical chemistry results revealed elevated CRP (29.50 mg/L), hypoalbuminemia (3.20 g/dL), low BUN (5.80 mg/dL), and elevated fibrinogen (379 mg/dL). The significant increase in CRP is likely due to inflammation from pneumonia. Hypoalbuminemia could be due to swallowing difficulties during the crisis, affecting nutritional intake, and the pneumonia infection might also reduce liver albumin production. Inadequate nutritional intake may explain the low BUN, and the elevated fibrinogen is likely related to the inflammation involved in both myasthenia gravis and pneumonia.[10,11]

The patient's blood gas analysis revealed a mixed acid-base disturbance—respiratory acidosis and metabolic alkalosis—consistent with an autoimmune disease and myasthenic crisis resulting in dyspnea. Respiratory failure in myasthenic crisis can manifest as hypoxemia, hypercapnia, or both, due to impaired airway protection, inadequate secretion clearance, and hypoventilation. Bulbar muscle weakness disrupts cough, swallowing, and breathing reflexes, causing oropharyngeal secretion accumulation, airway obstruction, and an increased risk of microaspiration, atelectasis, upper airway resistance, and altered breathing patterns. Respiratory muscles fail to maintain adequate tidal volume, resulting in rapid, shallow breathing, reduced functional residual capacity, and increased respiratory effort, worsening respiratory muscle weakness and leading to hypoxia and hypercapnia, which are key pathophysiological features of myasthenic crisis.[10,11] Electrolyte tests showed hypokalemia, hyponatremia, and hypocalcemia, likely due to neuromuscular junction dysfunction causing electrolyte dysregulation, especially potassium.[1,11]

Therapeutic plasma exchange (TPE) is the primary treatment for myasthenic crisis. TPE performed 5-6 times effectively reduces symptoms, with improvement often noted within four days post-TPE. TPE reduces AChR antibodies and is recommended for patients with severe symptoms, such as respiratory distress, swallowing difficulties, and impaired locomotor function. The typical TPE regimen includes daily plasma exchange at 1 to 1.5 plasma volumes for 5 or 6 days, with 5% albumin as the replacement fluid.[5,6,12] In this case, TPE was administered at a dose of 200-250 ml/kg body weight in 5 sessions. During the first TPE session, the patient developed urticaria on all

extremities as a TPE complication.

Studies on pediatric and adult patients report varying TPE-related complication rates. A retrospective study by Lu et al. in Sweden reported a 4.3% complication rate among adult TPE patients, while Mokrzycki et al. reported a 5-12% complication rate. Common complications include hypotension, perioral sensory abnormalities due to hypocalcemia, muscle spasms, headaches, and urticaria. Most TPE-related complications are mild but can be fatal.[13]

Several factors contribute to TPE complications, including the type and volume of replacement fluid, anticoagulant choice, vascular access, and plasma separation method. Studies show a higher incidence of side effects with fresh frozen plasma compared to other replacement fluids like 5% albumin. Allergic reactions can range from mild fever and urticaria to severe reactions like laryngospasm.[7,13,14]

In this case, the patient developed a Type I hypersensitivity reaction with urticaria after TPE with albumin. Type I hypersensitivity involves a specific antigen-antibody (IgE) reaction on mast cells. Mast cells and basophils release pharmacologic mediators that affect various organs. Post-TPE hypersensitivity may involve mast cell or basophil mediator release triggered by IgE, complement factors, or immune complex formation.[15–18]

The first mechanism is IgE-mediated anaphylaxis, where IgE-coated mast cells release mediators upon allergen exposure, leading to clinical manifestations like urticaria, angioedema, asthma, and anaphylaxis.[15,18] Another mechanism is immune complex-mediated or complement-mediated anaphylaxis, where immune complexes or complement proteins activate mast cells to release inflammatory mediators.[15,18] The third mechanism involves direct mast cell or basophil activation by albumin, where albumin as an allergen directly stimulates mast cell degranulation.

In this case, antihistamines—10 mg intravenous diphenhydramine and 10 mg oral cetirizine every 12 hours—were administered to treat the hypersensitivity reaction. After antihistamine administration, the patient's urticaria improved, and the second and third TPE sessions proceeded without further hypersensitivity reactions.

This case uses a unique topic regarding type-I hypersensitivity reactions that occur after TPE in a patient with Myasthenia Gravis (MG) crisis. This topic is rarely discussed so this case report can lead to recall bias, where patients and physicians more easily remember unusual outcomes or presentations. Weakness of case reports can lead to recall bias, where patients and physicians more easily remember unusual outcomes or presentations.

CONCLUSION

A case was reported of a 56-year-old woman diagnosed with myasthenia gravis (MGFA grade V) experiencing a myasthenic crisis and Type I hypersensitivity urticaria following therapeutic plasma exchange (TPE). Diagnosis was based on history, physical examination, and supporting tests. She presented with shortness of breath and had a history of myasthenia gravis since 2010. During TPE with albumin to manage her crisis, she developed a hypersensitivity reaction with urticaria on all four limbs. Laboratory tests showed normal hematology, elevated CRP and fibrinogen, hypoalbuminemia, and low BUN. Blood gas analysis indicated mixed respiratory acidosis and metabolic alkalosis, along with electrolyte imbalances of hypokalemia, hyponatremia, and hypocalcemia. Chest X-ray suggested pneumonia, a precipitating factor for the crisis. Treatment included intubation, IV NaCl 0.9%, methylprednisolone, pyridostigmine, levofloxacin, KCl drip to manage hypokalemia, TPE albumin at 200-250 ml/kg body weight in 5 doses, and diphenhydramine and cetirizine for hypersensitivity, with intravenous diazepam for seizures. Further studies are needed with different study designs and larger samples for future development of this topic.

DISCLOSURES

Ethical Considerations

None.

Conflict of Interest

The authors have no conflict of interest.

Author Contribution

All authors similarly contribute to the thinking about from the investigate concepts, information acquisitions, information investigation, factual investigations, changing the paper, until detailing the consideration comes about through publication.

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