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Adjunctive Use of Plasmapheresis and Intravenous Immunoglobulin Therapy in Sepsis: A Case Report

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In the United States, approximately 750 000 cases of severe sepsis occur each year, and more than 210 000 cases result in death.[1,2] Although the prevalence of sepsis continues to increase, the mortality rate of 28% to 50% remains unchanged.[1,2] Sepsis causes disturbances of homeostasis that lead to excessive coagulation, systemic inflammation, and impaired fibrinolysis.[3] In addition, blood flow to organs can be reduced despite adequate cardiac output because an imbalance occurs between coagulation and fibrinolysis, resulting in impaired tissue perfusion.[3]

Traditional treatment of sepsis includes control of the source of infection, intravenous antibiotic therapy, aggressive replacement of fluids, inotrope and/or vasopressor therapy, as well as supportive therapies such as mechanical ventilation, strict glycemic control, and measures to prevent infection.[3] Survival in patients with sepsis depends on recovery at a microcirculatory level that allows impaired organs to function normally again. Experimental therapies such as treatment with anti-inflammatory agents, antiendotoxins, and anticytokine medications have resulted in little improvement in survival.[4] A newer therapy, administration of drotrecogin alfa (activated), treats the pathophysiological consequences of severe sepsis: inflammation, coagulation, and impaired fibrinolysis. Drotrecogin alfa (activated) has been effective in patients with evidence of a systemic inflammatory response and organ dysfunction, but use of the agent increases the risk of bleeding and so its appropriateness must be determined on an individual basis.[5]

Plasmapheresis has been available for decades and is most commonly used in treatment of systemic lupus erythematosus, myasthenia gravis, sickle cell crisis,[6] and oncological disorders such as lymphoma and multiple myeloma.[7] More recently, plasmapheresis has been used in the treatment of sepsis associated with necrotizing soft tissue infections (NSTI) caused by both aerobic and anaerobic organisms. According to Harborview Medical Center's institutional guidelines (Table 1), patients with NSTI caused by proven clostridial, streptococcal, or staphylococcal infections with or without toxic shock syndrome may receive plasmapheresis. However, plasmapheresis should not replace aggressive surgical debridement, which should be the primary therapy before plasmapheresis is considered.

Table 1 Institutional indications for plasmapheresis in patients with necrotizing soft tissue infection

Patient must have one of the following:
White blood cell count >30.0 x 10^9/L
Serum creatinine level >177 µmol/L (2 mg/dL) at time of admission
Hypotension with systolic blood pressure <90 mm Hg or dependence on inotropes and/or vasopressors
Acute respiratory failure

Plasmapheresis removes harmful substances produced by the infecting organism and/or the excessive inflammatory response.[6] Two methods are used to separate plasma from blood cells: membrane filtration and extracorporeal centrifugation. Both techniques are designed to remove large molecular weight substances from the plasma.[6] Examples of these substances include plasma proteins such as albumin and immunoglobulins, pathogenic autoantibodies, clotting factors, endotoxins, and proinflammatory cytokines.[8]

Plasmapheresis removes large, harmful molecules such as pathogenic autoantibodies, endotoxins, and proinflammatory cytokines.

Plasmapheresis is also known as plasma exchange because the plasma removed is replaced with albumin, fresh frozen plasma, or crystalloid fluid. Changes in

prothrombin time and activated partial thromboplastin time are modest unless the patient's fibrinogen level is low. If fresh frozen plasma is not the replacement fluid, it is essential to monitor patients for signs and symptoms of coagulopathy because plasma, some white blood cells, and platelets are removed during plasmapheresis.[7] The prothrombin time and activated partial thromboplastin time should typically revert to normal within 24 hours. In patients with coagulopathies, it might be necessary to use fresh frozen plasma rather than albumin or crystalloid fluid to replace the fluid removed during plasmapheresis.

Plasmapheresis may be used to treat sepsis related to necrotizing soft tissue infections.

In addition to plasmapheresis, supplemental use of intravenous immunoglobulin (IVIg) has been beneficial in patients with sepsis who are immunocompromised.[9] Furthermore, use of IVIg may prevent postoperative infections,[10] and IVIg is used in the treatment of various bacterial infections. IVIg is a mixture of proteins containing γ-globulins or antibodies, predominantly IgG, which provide humoral immunity against disease. Infusion of IVIg provides passive, temporary immunity for the body. It is used in the treatment of several diseases, including a variety of immunodeficiencies and autoimmune disorders, such as acute and chronic autoimmune thrombocytopenic purpura, mucocutaneous lymph node syndrome, and chronic inflammatory demyelinating polyneuropathy.[11] Treatment with IVIg remains controversial in the treatment of sepsis because of the cost and the scarcity of the product and because adequate dosing has not yet been established.

The purpose of IVIg administration in severe sepsis is to increase serum levels for a minimum of several days to the upper reference range or higher.[12] Patients with sepsis often have serum levels of immunoglobulin in the lower reference range. Furthermore, the occurrence of postoperative infection is influenced by low levels of IgG and IgM.[13] Use of IVIg in addition to plasmapheresis is determined by the surgical and/or critical care team. If IVIg is used, it should be given after plasmapheresis, because it would be removed during plasmapheresis.

Most of the research available on use of plasmapheresis and IVIg in patients with NSTI and/or toxic shock syndrome indicates that this combination provides some improvement in these patients. However, no large controlled trials have been done that would provide statistical support for the clinical efficacy of this combination of therapies. In addition, in a MEDLINE search, we found no published research on the combined use of plasmapheresis and IVIg for treatment of sepsis due to NSTI or toxic shock syndrome.

Intravenous immune globulin provides passive, temporary immunity for patients with sepsis, who frequently have serum globulin levels in the low normal range.

Case Report

MF, a 64-year-old woman, came to the emergency department because she had abdominal pain. Three weeks before admission, she had had intermittent pain that resolved, causing her not to seek further treatment. On the day of admission, she had persistent, severe abdominal pain with fever, chills, diarrhea, decreased appetite, and severe erythema of the abdominal wall. Computed tomography revealed a fluid-filled sac in both lower quadrants of the abdomen, indicating infection and bowel perforation with spillage of contrast material into the abdominal cavity.

MF underwent an exploratory laparotomy, ventral hernia repair, and small-bowel resection with primary anastomosis. The abdomen was left open to allow for additional debridements and washouts of necrotizing fasciitis of the abdominal wall. Postoperatively, blood cultures were positive for gram-positive rods, and ultimately severe sepsis due to clostridium developed. Triple antibiotic therapy of penicillin, gentamicin, and clindamycin was started. Twelve hours after surgery, plasmapheresis was performed in the burn intensive care unit. For sedation, MF was given a continuous propofol infusion with occasional intravenous boluses of fentanyl. This regimen was changed to morphine and lorazepam as needed, keeping MF comfortable but allowing her to follow commands.

Before and throughout plasmapheresis, MF received infusions of vasopressin and norepinephrine to promote hemodynamic stability. An insulin infusion was administered to maintain blood glucose levels between 80 and 110 g/L. Aggressively treating stress-induced hyperglycemia helps suppress the inflammatory response and improve myocardial function and thus is beneficial in sepsis and septic shock.[13] A maintenance infusion of isotonic sodium chloride solution was infused at a rate of 150 mL/h with occasional boluses of isotonic crystalloid compatible with blood products

Table 2 Laboratory results related to plasmapheresis*

Laboratory test	0-6 hours before procedure	During procedure	Hours after procedure			
			0-2	>2-4	>4-8	12-24
Lactate, mmol/L	1.5					0.5
Arterial pH	7.30	7.19			7.35	
White blood cell count, No. of cells x 10^9/L	13.3			11.0	6.1	
Prothrombin time, seconds	19.1-18.3		32.4	28.5	19.2	17.0
International normalized ratio	1.5		3.1	2.6	1.6	1.4
Hematocrit, proportion of 1.0	0.30			0.26	0.30	0.32
Fibrinogen, g/L	5.4		1.4	1.5-1.8	2.6	3.4
Platelet count, No. of cells x 10^9/L	184			119	82	
Urea nitrogen, mmol/L (mg/dL)	3.2 (9)				2.1 (6)	1.8 (5)
Creatinine, µmol/L (mg/dL)	62 (0.7)				71 (0.8)	71 (0.8)

*Empty cells indicate no analysis at this time.

for episodes of hypotension. A total of 3 units of fresh frozen plasma and 1 unit of red blood cells were administered to promote normal hemostasis before the insertion of an arteriovenous shunt for hemodialysis, which is necessary for plasmapheresis. One hour before plasmapheresis, MF's central venous pressure was 22 mm Hg, lactate level was 1.5 mmol/L, and white blood cell count was 13.3 x 10^9/L. Urine output was 25 to 50 mL/h. The results of laboratory studies, including coagulation tests, were unremarkable (Table 2). Plasmapheresis was performed without complication.

MF's hemodynamic condition remained stable during the procedure (Table 3). A total of 1.3 plasma volumes were replaced. A decrease in arterial pH occurred; however, the cause of the decrease is unknown. According to the transfusion service protocol, the replacement of 1.3 plasma volumes results in an exchange that removes approximately 60% of the inflammatory mediators present in a patient's plasma. During plasmapheresis, 4492 mL of MF's plasma was removed. Replacement fluid consisted of 245 mL of isotonic sodium chloride solution and 4437 mL of a 5% solution albumin. MF did not have further signs or symptoms of acidosis or poor tissue perfusion during or after plasmapheresis.

After plasmapheresis, 84 g of IVIg was delivered as a continuous infusion. Within the first 4 hours after plasmapheresis, MF was given an additional 4 units of fresh frozen plasma and 1 unit of red blood cells that resulted in increases in prothrombin time, international normalized ratio, and activated partial thromboplastin time and a decrease in hematocrit (Table 2). Her white blood cell count decreased to 11.0 x 10^9/L. Within 8 hours of treatment, MF's hemodynamic status improved, and she was weaned from the vasopressin, norepinephrine, and insulin infusions (Table 3). Her urine output was 80 to 175 mL/h, and her central venous pressure was 14 to 18 mm Hg. Throughout plasmapheresis and within 12 hours after treatment, no changes in respiratory status occurred. Ventilator settings remained unchanged, with the fraction of inspired oxygen at 0.40. No change in static pressure, static compliance, or mean airway pressure occurred. Oxygen saturation remained 98% to 100%. Chest radiographs revealed bibasilar atelectasis before and within 12 hours of plasmapheresis, with minimal improvement within 24 to 36 hours after plasmapheresis.

In summary, MF required less vasopressor support and had decreased inflammation and normal coagulation and hemostasis after a single session of plasmapheresis and IVIg therapy. Traditional therapies such as intravenous antibiotic therapy, supportive mechanical ventilation, and measures to prevent infection were continued. Glycemic control was maintained without the need for an insulin infusion. Parenteral nutrition was chosen rather than enteral nutrition because of the location of the abscess, repair of the small-bowel perforation, and need for frequent surgical debridement. MF returned to the operating room 5 times for washouts of her open abdomen within the first week after admission. She was transferred to an acute care unit on postoperative day 7 after a delayed primary closure of the midline laparotomy incision. The incision in the right lower quadrant was left open for healing by secondary intent. Mafenide wet-to-dry dressings were applied every 12 hours. MF had an ele-

Table 3 Hemodynamics related to plasmapheresis treatment

Vital sign	0-6 hours before procedure	During procedure	Hours after procedure				
			0-2	>2-4	>4-8	>8-12	>12-24
Systolic blood pressure, mm Hg	76-100	120-140	126-138	111-124	94-100	86-100	100-120
Diastolic blood pressure, mm Hg	58-66	74-75	75-79	62-73	56-60	43-46	60-70
Heart rate, beats per minute	60-68	80-82	74-90	72-79	70-72	86-91	80-94
Body temperature, ˚C	33.7-34.9	35.0	No documentation	35.2	36.1	36.1-36.5	36.5-37.6
Mean arterial pressure, mm Hg	65-89	80-90	92-99	78-90	69-80	63-81	66-85
Central venous pressure, mm Hg	22	17	No documentation	14	No documentation	14-18	14

vated white blood cell count of 24.0 x 10^9/L, but it slowly diminished once the mafenide dressing changes were implemented. The count was almost normal 20 days after the initial surgery. Thirty days after the initial surgery, a primary closure of the right side of the abdomen was accomplished. At 33 days after surgery, the white blood cell count normalized and remained at less than 10.0 x 10^9/L.

MF was discharged to home on postoperative day 40 without any detectable cardiac, pulmonary, or neurological impairment or long-term disability. We have no information about her long-term quality of life and functional status.

Conclusion

Early recognition and prompt treatment of severe sepsis are essential and play an important role in this challenging disease. Adjunctive plasmapheresis and IVIg may decrease mortality and improve outcomes when used for the treatment of severe sepsis related to NSTI. The development of these treatments will depend on an enhanced knowledge of the substances removed and replaced during plasmapheresis. Both therapies are still considered experimental and controversial, and further controlled clinical trials are needed to evaluate their efficacy in the treatment of sepsis.

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