EXPERIENCE WITH POLYCLONAL IMMUNOGLOBULIN THERAPY IN POLY TRAUMA PATIENTS WITH SEVERE SEPSIS

Sarfraz Khan Janjua, Raja Mushtaq Hussain, Syed Tariq Mohsin, Azhar Iqbal, Ahmad Hussain Mishwani, Muhammad Atif, Rizwan Hashim*, Khalid Mehmood

Combined Military Hospital Peshawar, *Army Medical College Rawalpindi

ABSTRACT

Objective: To evaluate the effects of intravenous immunoglobulin therapy on progression of severe sepsis in patients of poly trauma.

Design: Quasi-experimental study.

Place and Duration of Study: Combined Military Hospital Peshawar from June 2008 to Dec 2009.

Patients and Methods: Forty six patients of poly trauma with severe sepsis were included. Along with the standard management i.e., surgical management, fluid resuscitation, antibiotics, analgesics, ionotropic, ventilatory and nutritional support, IVIG 5% (intravenous immunoglobulin) was infused over a period of 6 hours and repeated for three consecutive days. Sequential Organ Failure Assessment (SOFA) score was used to assess the progress in all the patients.

Results: At the time of enrolment mean SOFA score was 5.41±1.127 and on the 15th day it was 1.62±2.24, mean age was 39.21+10.26 years. Thirty four patients (73.91%) developed gram negative sepsis and eighteen patients (39.13%) developed septic shock. Mean duration of stay in ICU and on ventilatory support was 20.80+9.61 and 10.52+5.52 days respectively. Thirty five days mortality rate of these patients was 30.43%.

Conclusion: The IVIG administration, when used along with the standard management appears to improve significantly the prognosis in patients of poly trauma with severe sepsis.

Keywords: Intravenous, Poly trauma, Severe sepsis, SOFA score.

INTRODUCTION

Sepsis in surgical patients continues to have high morbidity and mortality (30-50%) despite the development of new and powerful antibiotics[1]. Multi Organ Failure (MOF) is a major cause of morbidity after severe injury. Recent studies in ICU trauma patients have found an incidence of MOF between 5% and 25%. Mortality rate from ARDS alone is 40-50%, once additional organ system dysfunction occurs, the mortality rate increases to 90%[2].

Insufficient antibody response in critically ill patients, particularly those undergoing surgical procedures, could be due to failure of T cell-mediated help. It results in insufficient secretion or activity of cytokines ,required for adequate B cell activation, proliferation, or differentiation into immunoglobulin (Ig)-secreting cells i.e. plasma cells. Diminished levels of IgG, IgA, and IgM have been reported after trauma and major surgical procedures[3]. In patients with sepsis, favorable outcome seems to be closely associated with antibody levels against the causative pathogen[4]. Passive immunotherapy with intravenous immunoglobulins (IVIG) may represent a logical attempt to restore normal levels of antibodies directed against common pathogens and to enhance the function of polymorphonuclear and Kupffer cells[5,6]. In this descriptive study, the effects of polyclonal intravenous immunoglobulin therapy (IVIG) in young adult patients of poly trauma with severe sepsis were evaluated by Sequential Organ Failure Assessment (SOFA).

Correspondence: Lt Col Sarfraz Khan Janjua, Classified Anaesthetist, CMH Peshawar

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PATIENTS AND METHODS

This quasi-experimental study was carried out at Combined Military Hospital (CMH) Peshawar from Jun 2008 to Dec 2009. After approval by the hospital ethics committee, we enrolled fifty cases of trauma with severe sepsis according to the 1992 ACCP/ SCCM sepsis criteria[7] (temperature> 38°C or <36°C, heart rate >90 beats/min, respiratory rate >20/min or $PaCO_2$ < 32 mmHg, white blood

cell count >12,000/mm^3 or <4000/mm^3, documented infection and dysfunction of an organ). Septic shock was diagnosed when severe sepsis was associated with hypotension (systolic blood pressure <90 mmHg or a reduction of >40 mmHg from baseline, in the absence of any other cause for hypotension). The exclusion criteria were, irreversible end-stage organ damage, Glasgow coma score of 3/15, heart failure with grade IV dyspnoea and if the patient died before the completion of immunoglobulin therapy.

The initial management consisted of fluid resuscitation, analgesia and anti tetanus prophylaxis. The required surgical procedures were performed along with standard antibiotic therapy (Inj Cefuroxime 1.5 gm twice daily, Inj Metronidazole 500mg and Inj Amikacin 500 mg 8 hourly) which were changed subsequently according to the culture and sensitivity reports of the appropriate samples. After the initial management, Polyclonal IVIG 5% (intravenous human immunoglobulin) was started on the day of diagnosis of severe sepsis, 5 ml/kg per day IVIG 5% (50mg/ml i.e 250mg/kg) was infused intravenously over a period of 6 hours and repeated for three consecutive days.

Electrocardiogram, pulse oximetry, arterial blood pressure, central venous pressure and nasopharyngeal temperature were monitored continuously. Dopamine, dobutamine, epinephrine and/or norepinephrine were used to treat hypotension that was unresponsive to volume resuscitation. The aim was to achieve a central venous pressure of 5–10 mm of Hg. Blood samples for arterial blood gases, glucose, serum creatinine, serum bilirubin, complete blood count and coagulation profile were tested daily for 15 days. Transfusions of red cell concentrates, fresh frozen plasma and platelets were administered as per requirements. Blood glucose was maintained in the range of 80-150 mg/dl by insulin therapy according to requirements. Considering the suboptimal availability of ICU trained staff, early tracheostomy was done in seven patients who required ventilatory support for more than three to five days. Sequential organ failure assessment (SOFA) score was used to assess the development and degree of organ failure over time in individual septic patients (Table-1). Duration of mechanical ventilation, length of stay in the intensive care unit, septic shock and 35 days mortality rate were recorded.

Data was analyzed using SPSS version 15. Descriptive statistics were used to describe the data. Paired sample t-test was used to compare pre and post therapy SOFA score and *p*-value <0.05 was considered as significant.

RESULTS

Fifty patients were included in the study but 4 patients were excluded during the course of study as 2 patients died before the completion of immunoglobulin therapy, one developed severe anaphylaxis with the 1st dose of immunoglobulins and another patient was excluded due to technical reasons. Therefore, 46 patients were finally included in the study. Thirty four (73.91%) patients had sepsis resulting from infection with gram-negative organisms mainly *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* and *Acinetobactor species*, 13.04% patients had growth of *Staphylococcus aureus*, 4.35% patients had growth of Methicillin Resistant *Staphylococcus aureus* (MRSA) and in 8.70% patients no growth of organisms was detected. Initial mean SOFA score was 5.41±1.13. On day 15 mean SOFA score was 1.62±2.24. There was improvement in mean SOFA score from day one to day fifteen after the start of immunoglobulin therapy ($p<0.001$) Fig 1. Fourteen (30.43%) patients died. Eighteen (39.13%) patients fulfilled the criteria of septic shock. Mean duration of mechanical ventilation was 10.52±5.52 days and mean duration of stay in ICU was 20.80±9.62 days (Table-2).

DISCUSSION

Sepsis is a clinical syndrome that complicates severe infection and is characterized by systemic inflammation and widespread tissue injury. It is a major cause of morbidity and mortality in critically ill adults[1]. Multiple Organ Dysfunction Syndrome (MODS) is defined as a clinical syndrome where the development of progressive and potentially reversible physiological

dysfunctions in 2 or more organs or organ systems induced by a variety of acute insults including sepsis are characteristic and it is a process rather than an event[2]. Although numerous advances in the management of critically ill patients with severe infections have occurred in recent years, the mortality rate associated with severe sepsis and septic shock remains unacceptably high at 30% to 50%[4]. Different anti-inflammatory treatment regimens such as anti-tumor necrosis factor, anti-platelet-activating factor, anti-interleukin-1, anti-endotoxin, anti-bradykinin, inhibitors of nitric oxide synthetase, steroids and activated protein C analogs have yielded disappointing results[8-10].

Because of its broad and potent activity against both bacterial products and host cytokines, polyclonal intravenous immunoglobulin (IVIG) has been investigated as an adjunctive therapy for treating severe infections. IVIG is an immunomodulator in that it balances by strengthening immune systems that are too weak and reducing activity in overactive immune system[6]. The activities or benefits of IVIG therapy include modulation of the immune chemical known as complement and suppression of the inflammatory chemicals, such as the cytokines, chemokines, and metalloproteinases[11]. Adverse effects are reported to occur in about 15% of patients receiving IVIG.

In this study, SOFA Score was applied to evaluate the effects of IVIG immunoglobulin treatment on progression of organ failure in patients of polytrauma with severe sepsis and septic shock. Several multiple organ dysfunction scoring systems have been developed but the SOFA score and the Multiple Organ Dysfunction Score are the most commonly applied. The SOFA score has been validated in trauma patients[12].

Mortality rate in patients under study was 30.43% that is less than the study by Dominioni et al[13]. In their study the mortality rate was reduced by administration of IVIG from 67% to 38% in postoperative septic patients having a sepsis score higher than 20. One of the possible reason for this difference could be relatively young patients in our study group (table 1). Our results are comparable to the study by Simru Tugrul et al[14] who have noted the septic shock incidence (38% versus 57%) and 28-days mortality rate (23.8% versus 33.3%) between the IgM enriched IVIG and control groups whereas in our study group the incidence of septic shock was 39.13%. Schedel et al[15] reported a statistically significant decrease in the APACHE II score beyond the 5th day after inclusion, as well as a decrease in the 6-week mortality rate (1/27 in the IgM enriched IVIG (Pentaglobin) versus 9/28 in the control group, in septic shock patients. The Cochrane group[16] analyzed 23 controlled clinical studies published between 1966 and 1999 and found that sepsis-related mortality was significantly reduced only in patients who received polyclonal IVIG in contrast to treatment with monoclonal antibodies and anti-cytokines in sepsis and septic shock. De Simone et al[17] used IVIG in patients with severe sepsis and obtained reductions in hospitalization, number of days on antibiotics and number of positive cultures. However the mortality rate in their study was 58% in IVIG versus 75% in control group.

Rodriguez et al[18] concluded that IVIG administration, when used in combination with adequate antibiotics, improved the survival of surgical ICU patients with intra-abdominal sepsis.

The initial fluid resuscitation, haemodynamic stability, proper and early surgical intervention and choice of adequate antibiotics have a dramatic impact on the outcome. The possible explanations for inconsistency of the literature include the nature and extent of injury, the delay before definitive treatment, the age and immunological status of the patients, the type, dosage and administeration schedule of immunomodulatory therapy. The use of different antibiotics, other treatment strategies, such as the use of catecholamines, corticosteroids and haemofilteration have the potential to interact and modify the response of the patients.

CONCLUSION

The addition of polyclonal immunoglobulins to the standard therapy appears to improve significantly the prognosis in patients with severe sepsis. Daily SOFA scoring is useful to assess the progress of the patients with severe sepsis and septic shock. However our results in this study do not make a clear contribution to the inconsistent results and recommendations on the use of immunoglobulin preparations in septic patients. Since multiple factors contribute to the outcome, a multi centre study is recommended to confirm the definite benefits of this adjunctive but expensive therapy.

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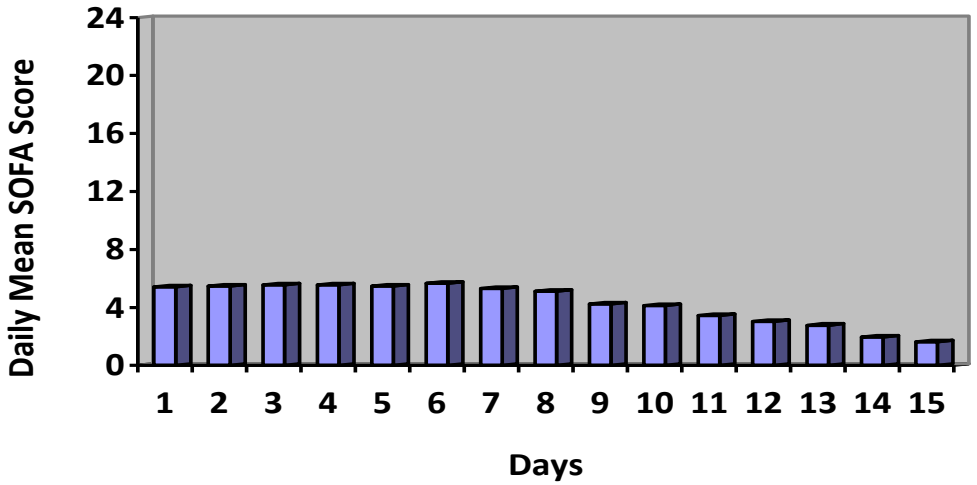

Figure: Description of daily mean SOFA score with time (n=46).

Table-1. Sequential organ failure assessment score (SOFA).

Respiratory System PaO_2/FiO_2 (mmHg), 19. < 400. 20. < 300. 21. < 200 and mechanically ventilated. 22. < 100 and mechanically ventilated.	**Nervous System Glasgow coma score,** 1. 13 – 14. 2. 10 – 12. 3. 6 – 9. < 6.
Cardio Vascular System. Mean Arterial Pressure or vasopressors required 1. MAP < 70 mm/Hg. 2. dopamine <= 5 or dobutamine (any dose). 3. dopamine > 5 OR epi <= 0.1 OR norepinephrine <= 0.1. 4. dopamine > 15 OR epi > 0.1 OR norepinephrine > 0.1. (vasopressor drug doses are in mcg/kg/min)	**Renal System Creatinine mg/dl or micromol/L (urine output).** 1. 1.2 – 1.9 mg/dl or 110—170 micromol/L. 2. 2.0 – 3.4 mg/dl or 171__299 micromol/L. 3. 3.5 – 4.9 mg/dl or 300—440 micromol/L (urine out put <500 ml/d). 4. 4.> 5.0 mg/dl or >440 micromol/L (urine out put <200ml/d)
Coagulation;Platelets×$10^3/\mu L$. 1. 1.2 – 1.9, (20----32) 2. 2.0 – 5.9, (33---101) 3. 6.0 – 11.9 (102---204) 4. > 12.0, (>204)	**Liver Bilirubin mg/dl (mic mol/L)** 1. 1.2 – 1.9, (20----32) 2. 2.0 – 5.9, (33---101) 3. 6.0 – 11.9 (102---204) 4. > 12.0, (>204)
TOTAL:	

Table 2. Demographic data and results (n=46).

Mean age years	**39.22 (+ 10.266)**
Gender(M/F)	41/5
Initial Mean SOFA Score	5.41(+1.12)
Gram Negative sepsis	73.91% (34)
Gram Positive	13.04% (6)
MRSA	4.35% (2)
No growth of organisms	8.70% (4)
Septic shock incidence	39.13 % (18)
Mortality	30.43%(14)
Stay in ICU days	20.80 (+9.61)
Mechanical ventilation days	10.52(+5.52)