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# Pentaglobin as Adjuvant Therapy for the Management of Sepsis in the Critical Care Unit

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## Abstract

**Background:** Sepsis is a life-threatening condition usually characterized by multiple dysfunctions, it is a medical emergency requiring prompt intervention. Since dysregulation of host factor response toward infection is the usual cause of sepsis or septic shock, pentaglobin regulate this process and improve survival, we aimed to investigate the effectiveness of pentaglobin as adjuvant therapy in the management of sepsis.

**Methods:** Prospective study that involved sixty patients with sepsis, these patients were enrolled to be treated with Pentaglobin (5 ml/kg/day) IV for three days in addition to the standard treatment regimen.

**Results:** 54 (90%) had survived, there was a significant reduction of their fever, white blood cell counts, tachycardia and tachypnea after treatment with pentaglobin. The most common sites of infection are the lungs. Finally, Gram-negative bacterial infections are the most common cause of sepsis.

**Conclusions:** The use of pentaglobin as an adjuvant therapy to the standard lines of management with sepsis is safe and beneficial.

**Keywords:** Pentaglobin; Treatment of Sepsis; Infection; Adjuvant

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## Introduction

Sepsis can be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Patients presented with infection can be assessed for poor outcome of sepsis using a bedside clinical score termed quick SOFA (qSOFA), if at least two of following are met: respiratory rate ≥22/min, altered mental status, or systolic blood pressure ≤100 mmHg (Table 1) [1].

Despite the introduction of new and more potent antibiotics, sepsis still has elevated mortality and morbidity rates. Failure of T cell-mediated immunity will lead to a reduction in the production and activity of the cytokines that active B cells, also it will reduce their proliferation and subsequent differentiation into immunoglobulin (Ig) secreting cells [2]. A favourable outcome for septic patients is related to the close correlation between the antibody levels against the causative pathogen [3].

Pentaglobin can neutralize endotoxins and exotoxins by scavenging active complement components and lipopolysaccharides, by stimulating opsonisation process and exerting a bactericidal activity in serum, by reducing pro-inflammatory mediators, and by increasing anti-inflammatory mediators [4].

Severe sepsis and septic shock are medical emergencies requiring prompt intervention guidelines for management that have been developed by a multinational multidisciplinary collaboration of experts as part of an education initiative known as the Surviving Sepsis Campaign, the latest iteration being the 2012 version. Many institutions have incorporated these therapies into "sepsis bundles" to promote best practice. Elements of sepsis management include initial resuscitation, diagnosis, antibiotic therapy, source control, and supportive therapy [5]. The current work aimed to investigate the effectiveness of pentaglobin as an adjuvant therapy in the management of sepsis.

## Methods

### Ethics and Consent

After prior approval from the Scientific Council of Anaesthesia and Intensive Care Board, written informed consent taken from patients or their first of kin, the study was conducted.

### Study Design and Setting

An observational prospective study, conducted from February 2017 to August 2017. The study carried out in a 15 bed mixed intensive care

**Table 1:** Criteria used to define organ dysfunction and organ failure (SOFA SCORE) [6].

| **Respiratory system:** **Pao2/FiO$_2$mmhg** | **1<400** | **2<300** | **3<200 On Mechanical ventilation** | **4<100 On Mechanical ventilation** |
|---|---|---|---|---|
| Nervous system: GCS | 13-14 | 10-Dec | 06-Sep | <6 |
| **Cardiovascular system :MAPr of administration of vasopressor required** | MAP<70 mmHg | dopamine<=5 | dopamine>5 or nor epinephrine<=0.1 | dopamine >15 or nor epinephrine > 0.1 |
| Liver: bilirubin(mg/dl) | 1.2-1.9 | 2.0-5.9 | 6.0-11.9 | >12.0 |
| Coagulation: platelet x10$^3$/mm$^3$ | <150 | <100 | <50 | <20 |
| Renal system: creatinine (mg/dl) | 1.2-1.9 | 2.0-3.4 | 3.5-4.9 | >5.0 |

**Table 2:** Assessment of demographic and clinical characteristics.

| **Variables** | **Value** |
|---|---|
| **Age (years), mean ± SD** | 43.53±19.64 |
| **Gender, n (%)** | |
| Female | 15 (25%) |
| Male | 45 (75%) |
| **Causative organism, n (%)** | |
| Klebsiella | 24 (40%) |
| Pseudomonas | 18 (30%) |
| Actinobacteria | 10 (16.7%) |
| Staphylococcus | 4 (6.7%) |
| Proteus | 2 (3.3%) |
| Enterobacter | 2 (3.3%) |
| **Organ failure, n (%)** | |
| Respiratory alone | 36 (60%) |
| Respiratory and CNS | 5 (8.3%) |
| Respiratory and renal | 7 (11.7%) |
| Respiratory and cardiac | 12 (20%) |
| **Fate after 28 days, n (%)** | |
| Survived | 54 (90%) |
| Death | 6 (10%) |
| **Positive CRP, n (%)** | |
| At baseline | 55 (91.7%) |
| After 28 days | 0 (0%) |
| **Positive Procalcitonin, n (%)** | |
| At baseline | 58 (97%) |
| After 28 days | 0 (0%) |
| CRP: C-reactive protein, n: number, SD: standard deviation, | |

unit (ICU) in a tertiary care referral hospital and academic institute in a Teaching Hospital.

All patient received adequate empirical antibiotic treatment (as defined by Cavazzuti et al) [7], in addition the all patients reeived pentaglobin (each 1 ml of pentaglobin contain approximatly 50 mg of plasma protein; which contains IgM 6 mg, IgA 6 mg, IgG 38 mg).

## Inclusion Criteria

Adult patient with sepsis in the ICU, all potentially eligible patients with sepsis were treated with pentaglobin as an adjuvant therapy in addition to the standard lines of management.

## Study Protocol

Following admission to the ICU, consecutive patients satisfying the inclusion criteria were included in the study. Our observations and analysis were disclosed to the ICU treating team. However, any alteration in clinical management based on our analysis was entirely at their discretion. The standard of care provided by combining the sepsis resuscitation intervention (6 hrs. bundles) and management interventions (24 hrs. bundles).

If indicated norepinephrine will be given as vasopressor, also if the need for inotropic arise dobutamine will be given.

Pentaglobin was given in the first day of sepsis (as part of 24h bundles) as an adjuvant therapy according to the local protocol of the unit. Pentaglobin given in a dose of 5ml/kg daily for 3 consecutive days.

## Data Collection

A complete work up of full investigations including WBC, Procalcitonin, C-reactive protein, blood culture and proper monitoring including: respiratory rate, heart rate, and temperature were taken as parameters during & post the uses of pentaglobin therapy. Demographic data (age & gender), diagnosis at ICU admission, days of stay in the ICU, and outcome at discharge were recorded for each patient.

## Statistical Analysis

Paired T test used to assess the degree of significance with p value less than 0.05 were considered significant. All analysis carried out using SPSS 22.0.0 (Chicago, IL).

## Results

Sixty patients involved in the study with an age range from 20-84 years and mean age of 43.53 ± 19.64 years. The most common type of microorganism was *Klebsiella* (40%), followed by *Pseudomonas* (30%) and *Actinobacter* (16.6%). Concerning organ failure, 36 patients was with respiratory failure (60%), 5 patients with Respiratory & CNS failure (8.3%), 7 patients with both respiratory and renal failure (11.7%), and finally 12 patient with both Respiratory and cardiac failure (20%).

The fate of the patients in the 28 days post treatment was 90% of patients survived. 91.7% of patients had positive CRP at the beginning, after treatment with pentaglobin all patients became CRP negative. 97% of patients had positive procalcitonin (PCT) at the beginning of the study, after treatment with pentaglobin all patients were found to have negative Procalcitonin as illustrated in table 2.

All variables-temperature, WBC count, pulse rate, and respiratory rate, were significantly reduced after 5 days of treatment with pentaglobin therapy, as illustrated in table 3.

## Discussion

Mortality rates of sepsis and septic shock remain elevated [8], which can be attributed to several factors which include delay in the early identifying symptoms of sepsis, insufficient resources and inappropriate application of guidelines [5]. The use of sepsis treatment bundles led to revolutionize outcomes in septic patients, recently the addition of pentaglobin to these bundles provided as promising treatment option since they have pleiotropic effect on bacteria and the host response to infection [9].

The study of Ilaria Cavazzuti et al conducted between two groups, patients that received adjuvant pentaglobin therapy compared to

**Table 3:** The Effect of Pentaglobin on different variables after 5 days.

| Variables | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | % change | p-value |
|---|---|---|---|---|---|---|---|
| **Temperature** | 38.35±0.44 | 37.98±0.46 | 37.67±0.46 | 37.42±0.46 | 37.42±0.49 | -2.43% | <0.001 |
| **WBC count** | 21.6±9.96 | 18.33±9.61 | 16.18±8.34 | 13.56±8.26 | 10.16±8.39 | -52.9% | <0.001 |
| **RR** | 28.9±5.78 | 24.63±4.85 | 20.67±5.24 | 17.87±6.17 | 14.7±7.15 | -49.1% | <0.001 |
| **PR** | 120.2±11.89 | 112.9±13.34 | 103.03±12.9 | 95.5±13.28 | 88.03±14.62 | -26.7% | <0.001 |
| WBC: white blood cell, RR: respiratory rate, PR: pulse rate | | | | | | | |

the patients that did not receive pentaglobin therapy. The overall mortality rate was reduced by 21.1% in those who received pentaglobin compared to patients who did not received pentaglobin. This is due to the refinement of immunity and decrease in inflammatory process [7].

The current study showed that 90% patients (who were treated by pentaglobin as an adjuvant therapy to patients with sepsis), had survived, which indicate a significant reduction of overall mortality, this goes with Alejandria MM, Lansang MA, et al studies that showed a significant effect on the overall mortality (relative risk of death RR= 0.64; 95% confidence interval CI=0.5-0.81) [10], and also pildal J, et al study showed a significant effect on mortality (RR=0.77, 95% CI=0.68-0.88) [11].

The overall mortality in critical care setting is multifactorial; hence some studies such Werdan et al revealed that there is no significant reduction effect on overall mortality [12].

The current work and of Ilaria Cavazzuti et al showed that the causes of deterioration were multi organ failure and refractory septic shock as compared with former improved group [7].

There were significant improvement in Procalcitonin and CRP from day one with starting pentaglobin to the fifth day. This indicates that pentaglobin treatment has an important role in the early stages of inflammatory and immune response to infection.

There were statistically significant improvement in systemic inflammatory response such as fever, and white blood cell counts in addition to the resolution of tachycardia and tachypnea from day 1 to day 5 in ICU with the initiation of the adjuvant therapy of pentaglobin, with a percentage of improvement (2.43%, 52.9%, 26.7%, and 49.1%, respectively). This goes with Berlot et al which observed beneficial effect in the same parameters [13].

The results showed that the most common type of microorganism in patients with sepsis were gram-negative bacterial infections (*Klebsiella pneumonia*, *pseudomonas aeruginosa*) and the percentage were (40%, 30%, respectively) and the common infection sites were lungs and abdominal cavities, this goes with Ilaria Cavazzuti et al. study which revealed the common type of microorganism was gram-negative bacteria and the common infection sites were lungs and abdominal cavities [7].

## Conclusions

The current study suggests that early adjuvant treatment with pentaglobin at a dose of 5 ml/kg per day for 3 days is safe and effective and lead to reduction in the risk of mortality in patients with sepsis. Significant improvement in systemic inflammatory response such as fever, procalcitonin levels, C reactive protein levels and white blood cell counts in addition to resolution of tachycardia.

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