

## The Role of Intravenous Immunoglobulin in Decreasing the Level of Procalcitonin in Early Phase of Sepsis: A Prospective Study

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### Abstract

**Background:** Intravenous immunoglobulin (IVIG) is used alongside antibiotics in the management of severe infections. Recent reports revealed that IVIG treatment has a mortality benefit in patients with severe sepsis and septic shock. On the other hand, procalcitonin (PCT) is used as biomarker for severe bacterial infections and sepsis. Therefore, we conducted this prospective study to evaluate the role of IVIG in decreasing the serum levels of PCT in the early phase of sepsis.

**Aim of Study:** To compare the efficacy of using IVIG in the treatment of patients with early sepsis.

**Patients and Methods:** Forty patients with early sepsis were enrolled in this study from February 2019 to January 2020 and randomly divided into two groups. Twenty patients were treated with commercially available human polyclonal IVIG 0.5gm/kg/day IV infusion for 3 consecutive doses (IVIG group) and twenty were managed with routine sepsis care according to recent guidelines (non-IVIG group).

**Results:** The majority of the study patients were males (62.5%). The IVIG and non-IVIG study groups were comparable in terms of age ( $p=0.33$ ) and baseline PCT levels ( $p=0.26$ ). We observed significant differences between the IVIG and non-IVIG study groups in terms of serum PCT levels, being significantly lower in the IVIG group at all the three time points ( $p=0.03$ ,  $0.002$ , and  $0.003$  at 1, 3 and 7 days of admission, respectively).

**Conclusion:** In conclusion, the use of IVIG at 0.5gm/kg/day IV infusion for three days was associated with significant reductions in serum PCT levels after one day, extending to one week of admission in patients with early sepsis. These results sum up with the evidence on the potential of IVIG in the treatment of early sepsis and larger, longer follow-up studies are recommended for confirmation.

**Key Words:** Sepsis – Septic shock – Intravenous immunoglobulin.

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### Introduction

**DIAGNOSING** and managing severe bacterial infections and associated multi-organ dysfunction in the ICU is a major dilemma in critical care medicine [1,2]. Sepsis occurs due to the host response to the pathogen [3]. In the last decades, sepsis become the most serious cause of hospitalization with increasing prevalence and mortality rates of 20-50% [1,4]. Although the death rate of septic shock is gradually decreasing as a result of advances in adjuvant therapies, it stays relatively high [5]. The pathogenesis of sepsis results from the imbalance in the coagulation and inflammation processes [6]. Therefore, regulating inflammation and coagulation is important to manage septic patients [7].

Intravenous immunoglobulin (IVIG) regulates the discharge of pro-inflammatory cytokines like tumor necrosis factor (TNF- $\alpha$ ), interleukin (IL-10), and high mobility group box-1 (HMGB1) [8,9]. It has demonstrated significant benefits in the treatment of inflammatory and autoimmune and diseases [7]. In addition, IVIG is used alongside antibiotics in the management of severe infections [10]. Recent reports revealed that IVIG treatment has a mortality benefit in patients with severe sepsis and septic shock [11,12].

Immediate sepsis diagnosis and prognostic evaluation may optimize the survival outcomes [13]. In the last decades, procalcitonin (PCT) was used as biomarker for severe bacterial infections and

### Abbreviations:

IVIG : Intravenous immunoglobulin.  
PCT : Procalcitonin.  
TNF : Tumor necrosis factor.

sepsis [14,15]. Procalcitonin, synthesized physiologically by the C cells of the thyroid gland, is a 116 amino acid protein and is a precursor for calcitonin hormone. In cases of sepsis and systemic inflammation, the serum level of PCT is markedly increased [16]. The production of PCT is initiated by pro-inflammatory cytokines [15,17]. Moreover, PCT has a pro-inflammatory effect on human monocytes and whole blood treated with PCT contained higher concentrations of pro-inflammatory cytokines [18].

Therefore, we conducted this prospective study to evaluate the role of IVIG in decreasing the serum levels of PCT in the early phase of sepsis.

### Patients and Methods

#### Study design:

The current study was an open-label, randomized, controlled trial which was performed at the Intensive Care Units (ICUs) of Saudi German Hospital in Madina, Saudi Arabia from February 2019 to February January 2020. The study's protocol was approved by responsible ethics committee. The manuscript was prepared according to the CONSORT statement recommendations [1]. We confirm that all study's procedures were in agreement with ethical guidelines in the 1975 declaration of Helsinki and applicable local regulatory laws. Informed, written consents were taken from all patient's guardians prior to study's enrollment.

#### Inclusion and exclusion criteria:

Patients >16 years old were enrolled if they acquired the early criteria of sepsis, including: Noradrenaline infusion  $\leq 0.1$   $\mu$ g/kg/min, total leucocytic count  $\leq 20,000/\text{mm}^3$ , PCT level  $\leq 2\text{ng/ml}$ , and Glasgow Coma Scale GCS  $\geq 13/15$ . Patients were excluded if they had autoimmune neurological diseases, thyroid carcinoma or small cell carcinoma, burns, or history of renal impairment.

#### Study arms and outcomes:

A total of 56 patients were screened for eligible inclusion. Finally, the current study included 40 patients with early sepsis: 20 treated with commercially available human polyclonal IVIG and 20 managed with routine sepsis care according to recent guidelines [13]. The IVIG dose was 0.5gm/kg/day IV infusion for 3 consecutive doses. The main outcome was the serum PCT level after 1,3 and 7 days of admission.

#### Statistical analysis:

Data analysis was done using the Statistical Package for Social Sciences (SPSS, version 24,

for PC; IBM, Armonk, NY). Data were stated as either frequencies (%) or means  $\pm$  standard deviations. The two study groups were compared using the Chi-Square test or the independent sample *t*-test. A *p*-value of less than 0.05 was considered significant.

### Results

#### Baseline characteristics:

We enrolled 40 patients with early sepsis in the current study. The majority of the study patients were males (62.5%). The IVIG and non-IVIG study groups were comparable in terms of age ( $p=0.33$ ). Both groups were similar in their mean weight ( $84.50 \pm 11.25$  vs.  $83.65 \pm 10.54$  years;  $p=0.78$ ) and the main cause of sepsis in both groups was chest disorders. Likewise, the difference between studied groups in terms of baseline serum lactate was not significant ( $p=0.43$ ) or CRP ( $p=0.74$ ). No significant difference was found between studied groups in terms of baseline PCT ( $p=0.26$ ). Table (1) illustrates the baseline characteristics of enrolled patients in the current study.

Table (1): The baseline data of study groups.

	IVIG (N=20)	Non-IVIG (N=20)	<i>p</i> - value
Male, No. (%)	12 (60%)	13 (65%)	0.99
Age (years), Mean $\pm$ SD	61.2 $\pm$ 14.9	55.35 $\pm$ 21.9	0.33
Weight (Kg), Mean $\pm$ SD	84.50 (11.25)	83.65 (10.54)	0.78
<i>Causes, No. (%)</i>			
- Abdomen	5 (25%)	7 (35%)	0.47
- Respiratory Infection	11 (55%)	10 (50%)	
- Urinary Tract infection	3 (15%)	3 (15%)	
- Others	1 (5%)	0	
Serum lactate (mg/dL), Mean $\pm$ SD	12.8 $\pm$ 6.5	13.4 $\pm$ 7.5	0.43
CRP (mg/dL), Mean $\pm$ SD	81.32 $\pm$ 74	85.57 $\pm$ 64.9	0.74
Procalcitonin (ng/mL)			
- Mean $\pm$ SD	1.5 $\pm$ 0.6	1.3 $\pm$ 0.68	0.26
- Range	(0.09-2)	(0.07-2)	

#### Serum PCT levels after treatment:

We observed significant differences between the IVIG and non-IVIG study groups in terms of serum PCT levels, being significantly lower in the IVIG group at all the three time points ( $p=0.03$ , 0.002, and 0.003 at 1,3 and 7 days of admission, respectively); Table (2). Moreover, across the follow-up period, we observed a significant difference between the serial measurements of serum PCT levels in the IVIG group ( $p<0.001$ ). However, no significant difference was recorded between the serial PCT measurements in the non-IVIG group ( $p=0.06$ ); however, a trend towards an increase was observed. Fig. (1) shows the serial measurements of serum PCT levels in both study groups.

There was no significant difference correlation between the degree of change in serum PCT and baseline age, weight, CRP, and serum lactate ( $p>0.05$ ).

Table (2): The changes in PCT level (ng/mL) over one week in the studied groups.

	IVIG (N=20)	Non-IVIG (N=20)	p-value
<i>After 1 day of admission:</i>			
- Mean±SD.	1.68±0.91	2.1±1.2	0.035
- Range	(0.08-3.5)	(0.09-5.6)	
<i>After 3 days of admission:</i>			
- Mean±SD.	1.14±0.61	3±2.24	0.002
- Range	(0.02-2.1)	(0.09-11.6)	
<i>After 1 week of admission:</i>			
- Mean±SD.	0.6±0.88	3.5±2.89	0.003
- Range	(0.02-3.7)	(0.03-12.9)	
<i>p</i>	<0.001	0.065	

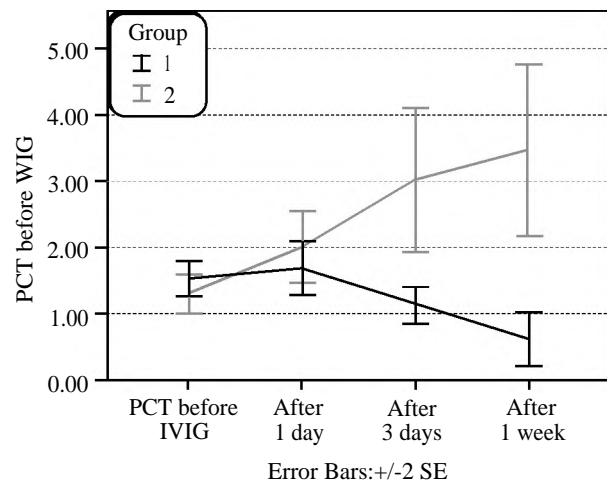


Fig. (1): Shows the serial measurements of serum PCT in IVIG (1) and non-IVIG (2) study groups.

### Discussion

The current study was aimed to test the efficacy of IVIG in early sepsis, using PCT as a marker for sepsis progression. Our results showed that IVIG treatment was associated with significant reductions in serum PCT levels in the serial measurements after 1,3, and 7 days of admission in comparison to the non-IVIG group. These results augment the evidence on the efficacy of using IVIG in the treatment of patients in the early phase of sepsis. Our results are in agreement with those of Ishikura et al., who showed significant reduction of PCT - among other parameters- after IVIG treatment [7].

The data on the efficacy of IVIG in sepsis treatment in the literature have been controversial. Although some studies have shown significant mortality benefits [7,20], the large SBITS study (n=653) showed that a dose of 0.9g/kg body weight

in total does not decrease mortality in patients with score-defined sepsis [21]. A Cochrane review of 43 studies revealed that the use of polyclonal IVIG lead to decrease in mortality among sepsis patients; however, such benefit was not observed in the subgroup analysis of trials with low risk of bias. Trials on IgM enriched IVIG were small and the evidence to support a robust benefit remains deficient [22]. Therefore, supportive therapy with IVIG-continue to be experimental and the 2012 sepsis campaign guidelines did not recommend the use of IVIG in sepsis or septic shock patients [13].

A number of issues were highlighted with the original trials on IVIG in sepsis. These trials did not take the following factors into consideration: Endogenous levels of immunoglobulin isotypes, presence of antibodies against the sepsis-causing microorganism, accuracy of antibiotic prescription, degree of patient immunosuppression, and the concentration and antimicrobial specificities of the antibodies contained in the IVIG batches. Another variable that was not considered was the timing at which IVIG was administered “The Window of Opportunity Concept” [23]. Our study focused on the early stage of sepsis and showed significant benefit in that regard; however, future studies should test the efficacy of IVIG in different stages of sepsis to generate clear guidelines on its efficacy in different patients.

The utility of PCT as a biomarker of diagnosis and prognosis in sepsis has been investigated before. A systematic review of 30 studies concluded that PCT is a good biomarker for early diagnosis of sepsis in critically ill patients. However, its results should be analyzed in relation to the medical history, physical examination, and microbiological assessment [24]. Regarding its utility with IVIG treatment, a former study by Murakami et al., showed that IVIG suppresses the release of pro-inflammatory cytokines in PCT-stimulated human monocytic cells [25]. Another study by Nakashima et al., reported that PCT levels can predict the response to infliximab in patients with IVIG-resistant Kawasaki disease [15].

There are some limitations in this study. First, the small number of patients enrolled limits the external validity of our findings. Second, the short follow-up period (one week) that should be extended in future studies. Third, the nature of the study being observational is essentially subjected to some forms of bias as selection bias and potential confounders. Moreover, further randomized controlled trials with adjustment in their findings to the confounding factors mentioned above are required.

In conclusion, the use of IVIG at 0.5gm/kg/day IV infusion for three days was associated with significant reductions in serum PCT levels after one day, extending to one week of admission in patients with early sepsis. These results sum up with the evidence on the potential of IVIG in early sepsis treatment and should be confirmed by larger, longer follow-up studies.

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*Declarations:*

- Ethics approval and consent to participate: The present study's protocol was registered by the local ethical committee of Saudi German Hospital in Madina, KSA. We confirm that all study's procedures were performed according to ethical guidelines of the 1975 declaration of Helsinki and applicable local regulatory laws. Informed written consents were taken from all patients prior to study's enrollment.
- Consent for publication: All authors reviewed the paper and agreed to publish it.
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## دور الغلوبولين المناعي الوريدي في خفض مستوى البروكالسيتونين في المرحلة المبكرة من تسمم الدم: دراسة مستقبلية

الخلفية: جنباً إلى جنب مع المضادات الحيوية في إدارة الالتهابات الشديدة. كشف التقارير الأخيرة أن استخدام الغلوبولين المناعي الوريدي فائدة في الوفيات في المرضى الذين يعانون من تسمم الدم الحاد والصمة التسممية. ومن ناحية أخرى، يستخدم البروكالسيتونين (PCT) كمؤشر حيوي للعدوى البكتيرية الشديدة وتسمم الدم. لذلك، أجرينا هذه الدراسة المستقبلية لتقييم دور العلاج بال IVIG في خفض مستويات PCT في الدم في المرحلة المبكرة من التسمم في الدم.

الهدف من الدراسة: لمقارنة فعالية استخدام IVIG في علاج المرضى الذين يعانون من تعفن الدم المبكر.

المرضى والطرق: تم تسجيل أربعين مريضاً يعانون من تسمم بالدم المبكر في هذه الدراسة وتم تقسيمهم عشوائياً إلى مجموعتين. عولج عشرين مريضاً بال IVIG متعدد النسيلة البشري المتوفير تجارياً ٠.٥ جم/كجم/اليوم لمدة ثلاث جرعات متتالية (مجموعة IVIG) وعشرون بالعلاج الروتيني لرعاية مريض التسمم بالدم وفقاً للإرشادات الحديثة (مجموعة NON-IVIG).

النتائج: غالبية مرضى الدراسة كانوا من الذكور (٦٢.٥٪). كانت مجموعات الدراسة قابلة للمقارنة من حيث العمر ( $p=٠.٣٣$ ) ومستويات PCT المبدئية ( $p=٠.٢٦$ ). لاحظنا فروقات ذات دلالة إحصائية بين المجموعتين في مستويات PCT في الدم حيث كانت أقل بشكل ملحوظ في مجموعة IVIG في جميع النقاط الزمنية الثلاث ( $p=٠.٠٠٢, ٠.٠٠٢, ٠.٠٠٢$ ) في أيام ١ و٣ و٧ أيام من القبول، على التوالي.

الخلاصة: في الختام، ارتبط استخدام IVIG ٠.٥ جم/كجم/يوم بالتنقيط الوريدي لمدة ثلاثة أيام بانخفاض كبير في مستويات PCT في الدم بعد يوم واحد، وتمتد إلى أسبوع من الدخول للرعاية في المرضى الذين يعانون من تسمم الدم المبكر. هذه النتائج تؤكد على إمكانات IVIG في علاج تسمم الدم المبكر ويوصى بدراسات بها متابعة أكبر وأصول.