Available online on 15.10.2022 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Research Article

Measurement of Protein C Levels among Sudanese Children and Infants with Sepsis at Khartoum state, 2022

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Article Info:

Article History:

Received 19 August 2022
Reviewed 17 Sep 2022
Accepted 24 Sep 2022
Published 15 Oct 2022

Cite this article as:

Mohamod ZM, Merghani MM, Babiker NE, Measurement of Protein C Levels among Sudanese Children and Infants with Sepsis at Khartoum state, 2022, Journal of Drug Delivery and Therapeutics. 2022; 12(5-S):54-58

DOI: http://dx.doi.org/10.22270/jddt.v12i5-s.5699

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Abstract

Background: Sepsis is a life-threatening condition that arises when the body's response to infection causes injury to its own tissues and organs.

Materials and methods: This was cross sectional study conducted at Baraah pediatric center, Khartoum, Sudan during the period from May 2022 to August 2022, to measure protein C level in Sudanese children and infants with Sepsis. 50 patients were selected as a case group (46% were female and 54% were male.), and apparently healthy donors were selected as control group. 2.8 ml of venous blood samples were collected in Tri Sodium Citrate Anticoagulant. CRP and the blood culture were done for all the patients. The protein C level was performed using Ichroma device.

Results: Protein C results revealed the mean of protein C in case was (63.7±8.9), and in the control group was(79.8±11.1), when compared protein C mean between case and control groups there was a highly significant decreased with (p value 0.00) Also in the case group there was an insignificant differences between protein C, age, gender, and culture, p value >0.05), . In addition the result showed insignificant correlation between protein C and CRP(p value ≥0.05). The most common types of isolated bacteria in sepsis patients was Klebsiella

Conclusion: The study concludes that there is a significant decrease in protein C level in patients with sepsis.

Keywords: protein C , CRP sepsis , bacteria , Klebsiella

INTRODUCTION

For the Ancient Greeks, sepsis referred to rot, decay, or putrefaction. Galen and Celsus described the signs of inflammation as peripheral vasodilatation, fever, pain, increased capillary permeability, and organ dysfunction. The modern concept of sepsis has focused on the human response to invading organisms[1] that arises when the body's response to infection causes injury to its own tissues and organs, this initial stage is followed by suppression of the immune system.[2,3]

Neonatal sepsis is a systemic infection (blood infection) occurring in infants within first 28 days of life and is a major cause of morbidity and mortality in newborns.[4,5] According to the international pediatric consensus conference of 2001, neonatal sepsis was defined as systemic inflammatory response syndrome in the presence of or as a result of suspected or proven infection with or without accompanying bacteremia, documented by a positive blood culture in the first 28 days of life .[6]

Protein C (PC) is the vitamin K-dependent zymogen of a serine protease with antithrombotic, anti-inflammatory, and pro fibrinolytic properties.[7] the protein C pathway plays a critical role in immunocompetent patients with sepsis because of its antithrombotic and anti-inflflammatory properties. The conversion of protein C to activated protein C (APC) is mediated through thrombin. Thrombin binds to thrombomodulin, a receptor on the endothelial cell, and the thrombomodulin-thrombin complex coverts protein C to APC. APC generation also requires a second endothelial cell receptor, endothelial protein C receptor (EPCR), which presents protein C to the thrombomodulin-thrombin complex.1 In sepsis, APC contributes to restoring homeostasis by counteracting the pro coaguable and pro inflammatory down-regulating inflammatory cytokines, respectively. This may explain why lower baseline levels of protein C in patients with sepsis are associated with a worse outcome[7]

In sepsis, activation of the extrinsic pathway combined with depression of the inhibitory mechanisms of coagulation and fibrinolytic system result in a procoagulant state that may lead to microvascular thrombosis and multi-organ dysfunction syndrome. protein C (PC) play a major role in the regulation of coagulation, shifting thrombin from procoagulant to anticoagulant. and PC plasma levels decrease in sepsis and, when low, predict high mortality in adults. At birth, PC and is present at approximately 20– 60% of adult levels. It might cause Newborns to be potentially susceptible to sepsis-induced disseminated intravascular coagulation. Little is known about the prognostic value of plasma PC levels determined in neonates with suspected sepsis. This study was

design to measure protein C level in Sudanese infants and children with sepsis.

MATERIAL AND METHODS

This was cross sectional, hospital base study, conducted at the laboratory of ALbraa paediatric centre at Khartoum state during the period of May 2022 to august 2022.

All patients attending ALbraa paediatric centre and diagnosed with sepsis during the aforementioned period were included. In addition to that, apparently healthy children with no history of thrombi or bleeding were selected as control group. Participants refuse to give consent, and those with previous history of bleeding, thrombi, under anticoagulant drugs were excluded from the study.

From each participant 2.8 ml of blood samples were collected in trisodium citrate anticoagulant container for protein C level measurement.

Ichroma™ protein C is fluorescence Immunoassay (FIA) for the quantitative determination of protein C in human whole blood / plasma. The test was used a sandwich immune detection method; the detector antibody in buffer binds to antigen in sample, forming antigen antibody complexes and migrates onto nitrocellulose matrix to be captured by the other immobilized-antibody on test strip. The more antigen in sample forms the more antigen-antibody complex and leads to stronger intensity of fluorescence signal on detector antibody, which is processed by instrument for ichroma™ tests to show protein C level in sample. The data was collected using pre-designed structural questionnaire; the demographic and clinical data concerning each participant was obtained from the registry data base office.

Participants was informed verbally in their simple language about the research, its benefits and method of sample collection, we were Provide privacy and confidentially for every participant, then their approval taken, and ethical approval was taken from ethical scientific committee and medical laboratory science of National University - Sudan.

RESULTS

Socio- demographic data

In the present study 100 samples were collected from the children, 50 of them were affected by sepsis and selected as case group, and 50 of them apparently healthy children were selected as control group. The case and control group had a same frequency in the age and gender; about 38% their ages were less than one month, 28% more than one year, 46% were female and 54% were male. CRP and the blood culture were done for all the patients. Regarding the isolated bacteria; 20% was Klebsiella, 18% was Pseudomonas, and only 8% was Staphylococcus aureus. On the follow up for 15 days about 40% of the patients were died. (Tables 1, 2, 3) (figures 1,2,3) .

Table 1: Distribution of age in study population

	Age	Frequency	Percent
Case	< 1 month	19	38.0
	1 month - 1 year	17	34.0
	> 1 year	14	28.0
	Total	50	100.0
Control	< 1 month	19	38.0
	1 month - 1 year	17	34.0
	> 1 year	14	28.0
	Total	50	100.0

Table 2: Distribution of gender in study population

	Gender	Frequency	Percent
Case	Male	27	54.0
	Female	23	46.0
	Total	50	100.0
Case (survivor)		30	60.0
Case (non survivor)		20	40.0
Control	Male	27	54.0
	Female	23	46.0
	Total	50	100.0

Table 3: Distribution of blood culture results

Blood culture	Frequency	Percent
E. coli	8	16.0
Staphylococcus aureus	4	8.0
Pseudomonas	9	18.0
Klebsiella	10	20.0
Proteus spp	1	2.0
Acinetobacteria	2	4.0
Candida	7	14.0
No growth	9	18.0
Total	50	100.0

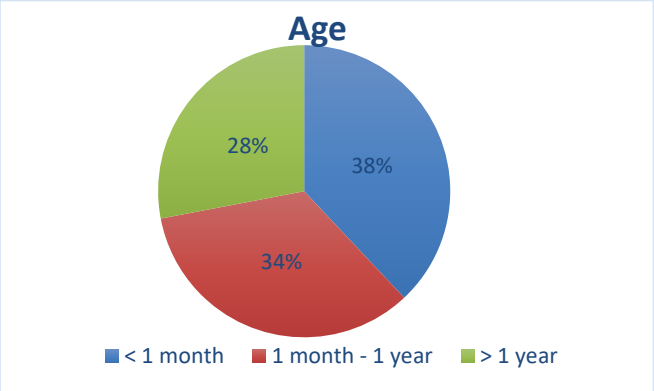

Figure 1: Distribution of age in the study population

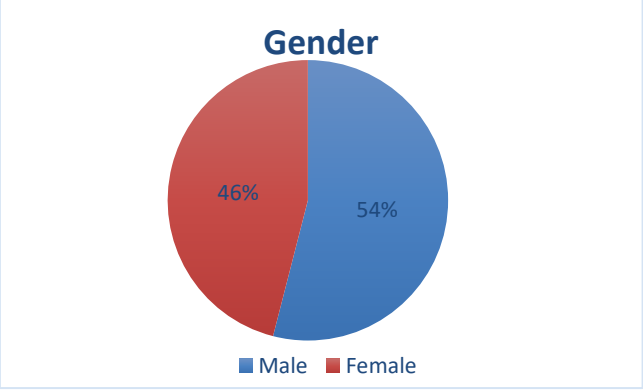

Figure 2: Distribution of gender in the study population

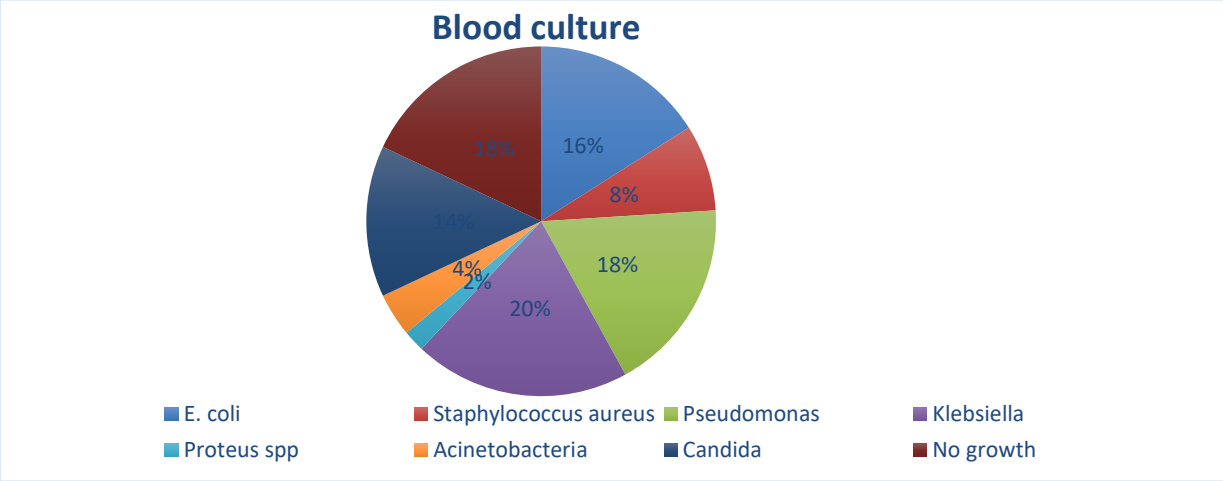

Figure 3: Distribution of blood culture results

Protein C and S results

Protein C results revealed; the mean of protein C in case was (63.7±8.9), and in the control group was(79.8±11.1), when compared protein C mean between case and control groups there was a highly significant decreased with (p value 0.00) , Also in the case group there was an insignificant differences between protein C, age, gender, and culture, p value >0.05), In addition the result showed insignificant correlation between protein C and CRP(p value ≥0.05) . (Table 4, 5, 6, 7, 8,9) (Figure4).

Table 4: Descriptive Statistics of study parameter

	N	Minimum	Maximum	Mean	Std. Deviation
Case					
Protein C	50	39	120	63.7	14.1
Control					
Protein C	50	65	111	79.8	11.1

Table 5: Comparison of Protein C between case and control

	Study population	N	Mean ± SD	P. value
Protein C	Case	50	63.6 ± 14.1	0.000*
	Control	50	79.8 ± 11.1	

Table 6: Comparison of Protein C according to age

	Age			P. value
	< 1 month (n=19)	1 month - 1 year (n=17)	> 1 year (n=14)	
Protein C	63.4 ± 14.1	64.3 ± 16.9	63.2 ± 10.9	0.972

Table 7: Comparison of Protein C according to gender

Parameter	Gender	N	Mean ± SD	P. value
Protein C	Male	27	64.0 ± 13.3	0.845
	Female	23	63.2 ± 15.3	

Table 8: Comparison of Protein C according to blood culture results

		N	Mean ± SD	Std. Deviation
Protein C	E. coli	8	57.7 ± 13.8	0.426
	Staphylococcus aureus	4	64.7 ± 2.1	
	Pseudomonas	9	59.7 ± 8.1	
	Klebsiella	10	66.9 ± 18.6	
	Acinetobacteria	2	54.0 ± 9.9	
	Candida	7	61.8 ± 6.1	
	No growth	9	72.3 ± 19.5	

Table 9: Correlations of CRP with protein C

		CRP
Protein C	Pearson Correlation	.250
	P. value	.080

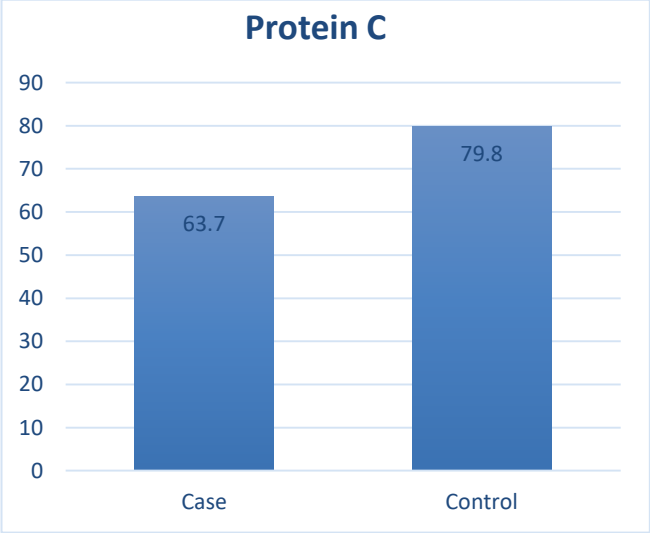

Figure 4: Mean of protein C in case and control

DISCUSSION

This was a cross sectional; hospital base study conducted in laboratory of Baraah children's hospital at Khartoum state during the period of May 2022 to august 2022. The study performed to measure protein C levels among Sudanese infants and children with sepsis by using florescence immune assay method.

In the present study for the case group about 38% their ages less than one month and 28% more than one year, the frequency of the gender was; 54% were males and 46% were females.

This finding was agreed with plunkett et al study which found that the incidence of severe sepsis in their cohorts was significantly higher in younger age groups. Also agree with study done by Bindle et al which revealed; male gender predisposes to severe sepsis and septic shock more than female (ratio 1.7), this effect has been ascribed to higher levels of testosterone. [8,9]

And disagree with Scott Watson etal which reported; Incidence of sepsis was the highest in infants, fell dramatically in older children (10- to 14-year-olds), and was 15% higher in boys than in girls.[10]

In this study CRP and the blood culture was done for all patients, also on the follow up for 15 days about 40% of the patients were died. similarly, P. Póvoa et al reported that Daily measurement of CRP is useful in the detection of sepsis and it is more sensitive than the currently used markers, such as BT and WBC. [11] One another study done by Cui et al indicatedthat; on the 2nd, 3rd, and5th days, serum CRP level was higher in the no survivorgroup than in the survivor group, and serum CRP has goodclinical prognostic value for patients with sepsis and septicshock. [12] But Xiaomeng Tang etal found , there was no significant differencein aspect of CRP level on PICU admission between non survivors and survivors patient in their study. [13] While Effat Hisamuddin et al stated that the CRP estimation does have a role in the diagnosis of sepsis but the test is not specific enough to be relied upon as the only indicator.

Regarding the isolated bacteria; 20% was Klebsiella, 18% was Pseudomonas, and only 8% was Staphylococcusaureus, this results consist with Kuruvilla *et al* results which found E.coli and Klebsiella were the most common organisms responsible for sepsis [14]. Also Movahedian et al found Pseudomonas and Klebsiell were the most prominent bacteria in sepsis[15]. In addition Zaidi *et al* suggested that Klebsiella species, E. coli, and S. aureus are major causes of infections in the first week of life [16]. While Gardner et al said E.coli is a common cause of sepsis while Pseudomonas, Klebsiell and Proteus were rare organisms in sepsis and S. aureas was unusual cause [17,18].

For the protein C level, the study results revealed; there was clearly decreasing in protein C with highly significant differences when compared between case and control group. In spite there was an insignificant difference when the protein C in cases compared with the age, gender, CRP and culture. In addition the result showed insignificant correlation between protein C and CRP. This agree with study done by Ryszard., et al showed that PC concentrations were significantly lower in neonates with sepsis[19]. Also agree with study done by Yan and Dhainaut et al which found more than 80% of patients with severe sepsis have decreased levels of endogenous protein C to below the lower limits of normal[20].

In addition Eliwan and *et al* revealed; that Protein C levels are reduced during pediatric and neonatal sepsis, which may play a major role in the development of disseminated intravascular thrombosis, purpura fulminans, and multiorgan dysfunction. [21].

Other agreement with study done by de Kleijn and *et al* which found ; Meningococcal septic shock in children results in high

mortality and morbidity, and decreased protein C levels in these patients are associated with a poor outcome. So their carried out a study based on using protein C as a treatment (protein C concentrate) is safe in children with purpura fulminans and meningococcal septic shock and leads to dose-related increases of plasma APC and resolution of coagulation imbalances[22.]

CONCLUSION:

The study concludes that there is a significant decrease in protein C level in patients with sepsis.

REFERENCES

1. Vincent J, Opal S, Marshall J, Tracey K. Sepsis definitions: time for change. The Lancet. 2013; 381(9868):774-775. https://doi.org/10.1016/S0140-6736(12)61815-7

2. Singer M, Deutschman CS, et al. "The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)". JAMA. 2016; 315(8):801-10. PMC 4968574. PMID 26903338. https://doi.org/10.1001/jama.2016.0287

3. Chao C, Muming Y, Yanfen C. "Pathological Alteration and Therapeutic Implications of Sepsis-Induced Immune Cell Apoptosis". Cell Death & Disease. 2019; 10(10):782. https://doi.org/10.1038/s41419-019-2015-1

4. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD., Early-onset neonatal sepsis. ClinMicrobiol Rev. 2014; 27(1):22-47. https://doi.org/10.1128/CMR.00031-13

5. Paolucci,M.,Landini, M.P and Sambri, V. How can the microbiologist help in diagnosis neonatal sepsis.IntJPediatr, 2012; 2012:120139. https://doi.org/10.1155/2012/120139

6. Goldstein SL ,sDutta ,Pgarcia, Hosptalized children .clinical journal of amarican society of nephrology 2015; 10(4):554-561 https://doi.org/10.2215/CJN.01900214

7- Kassam A, Chan A, Dzolganovski B, Constantin J, Ramphal R, Grant R et al. No Association Between Protein C Levels and Bacteremia in Children With Febrile Neutropenia. Journal of Pediatric Hematology/Oncology. 2009; 31(9):647-650 https://doi.org/10.1097/MPH.0b013e3181b1ec89

8. Bindl L, Buderus S, Dahlem P, Demirakca S, Goldner M, Huth R et al. Gender-based differences in children with sepsis and ARDS: The ESPNIC ARDS Database Group. Intensive Care Medicine. 2003; 29(10):1770-1773. https://doi.org/10.1007/s00134-003-1948-z

9. Plunkett A, Tong J. Sepsis in children. BMJ. 2015; 350 (jun09 10):h3017-h3017. https://doi.org/10.1136/bmj.h3017

10-.Scott Watson R, Joseph A. Carcillo, Walter T. Linde-Zwirble, Gilles Clermont, Jeffrey Lidicker, and Derek C. Angus. The Epidemiology of Severe Sepsis in Children in the United States. Respir Crit Care Med 2003; 67:695-701. https://doi.org/10.1164/rccm.200207-682OC

11- Póvoa, P., Almeida, E., Moreira, P. et al. C-reactive protein as an indicator of sepsis. Intensive Care Med1998; 24:1052-1056. https://doi.org/10.1007/s001340050715

12- Cui N, H. Zhang, Z. Chen, and Z. Yu, "Prognostic significance of PCT and CRP evaluation for adult ICU patients with sepsis and septic shock: retrospective analysis of 59 cases," The Journal of International Medical Research 2019; 47(4):1573- 1579 https://doi.org/10.1177/0300060518822404

13- Xiaomeng Tang, Lujing Shao, Jiaying Dou, Yiping Zhou, Min Chen,Yun Cui, Yucai Zhang , Chunxia Wang. Fibrinogen as a Prognostic Predictor in Pediatric Patients withSepsis: A Database Study. Mediators of Inflammation 2020; 1-10. https://doi.org/10.1155/2020/9153620

14- .Effat Hisamuddin, Aliya Hisam, Sughra Wahid, Ghulam RazaPak J Med Sci. 2015 May-Jun; 31(3):527-531

15- Kuruvilla K, Pillai S, Jesudason M, Jana A. Bacterial Profile of Sepsis in a Neonatal Unit in South India. Indian Pediatrics. 1998;35.

16- Movahedian A, Moniri R, Mosayebi Z. Bacterial Culture of Neonatal Sepsis. Short communication. 2006; 35(4):84_89.

17- Zaidi A, Thaver D, Ali S, Khan T. Pathogens Associated With Sepsis in Newborns and Young Infants in Developing Countries. Pediatric Infectious Disease Journal. 2009; 28(1):S10-S18. https://doi.org/10.1097/INF.0b013e3181958769

18- Gardner S. Sepsis in the Neonate. Critical Care Nursing Clinics of North America. 2009; 21(1):121-141. https://doi.org/10.1016/j.ccell.2008.11.002

19- Ryszard Lauterbach. Dorota Pawlik . Renata Radziszewska . Joanna Woźniak . Krzysztof Rytlewski. Plasma antithrombin III and protein C levels in early recognition of late-onset sepsis in newborns. Springer-Verlag. 2005; 165:585-589. https://doi.org/10.1007/s00431-006-0139-7

20- Yan S, Dhainaut J. Activated protein C versus protein C in severe sepsis. Critical Care Medicine. 2001; 29:S69-S74 https://doi.org/10.1097/00003246-200107001-00024

21- Eliwan H, Omer M, McKenna E, Kelly L, Nolan B, Regan I et al. Protein C Pathway in Paediatric and Neonatal Sepsis. Frontiers in Pediatrics. 2022; 9. https://doi.org/10.3389/fped.2021.562495

22. de Kleijn E, de Groot R, Hack C, H. Mulder P, Engl W, Moritz B et al. Activation of protein C following infusion of protein C concentrate in children with severe meningococcal sepsis and purpura fulminans: A randomized, double-blinded, placebo-controlled, dose-finding study. Critical Care Medicine. 2003; 31(6):1839-1847. https://doi.org/10.1097/01.CCM.0000072121.61120.D8