EVALUATION OF SERUM CALPROTECTIN AS A DIAGNOSTIC MARKER IN EARLY DETECTION OF NEONATAL SEPSIS

By

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ABSTRACT

Background: *Neonatal sepsis remains one of the main causes of mortality and morbidity despite the progress in hygiene so that the accurate and early diagnosis of neonatal sepsis is a relevant problem. Calprotectin is an antimicrobial, calcium and zinc binding heterocomplex protein that could be used as a nonspecific marker for activation of granulocytes and mononuclear phagocytes. Therefore, calprotectin has been proposed for the diagnosis of inflammatory conditions.*

Objectives: *The aim of this work was to evaluate the diagnostic value of serum Calprotectin in newborns with suspected sepsis.*

Patients and Methods: *After obtaining the approval of the Al-Azhar University Ethical Committee, A case control study was conducted on thirty neonates. The study was carried out in Al-Azhar University Hospitals (AL- Hussein &Sayed Galal Hospitals), during the period from June 2018 to October 2019. All patients gave their written informed consents prior to their inclusion in the study. Thirty children divided into 2 groups (case & control). Serum level of calprotectin was measured for all neonates recruited in this study, by a commercial ELISA assay*

Results: *Serum calprotectin levels were significantly higher in septic group than non-septic and control groups as mean Serum Calprotectin was 5.8 ± 1.4µg/ml and 1.3 ± 0.9µg/ml, respectively. Significant positive correlations were found between calprotectin levels and WBCs and IM ratio, while negative correlations were found between its level and lymphocytes and platelets. In our study, Calprotectin sensitivity and specificity values were 100 % and 97.5%, respectively.*

Conclusion: *Serum calprotectin levels were significantly higher in neonates with sepsis. Its levels correlated well with other laboratory markers of sepsis and neonatal mortality. It is a sensitive diagnostic marker for neonatal sepsis.*

Key Words: *Neonatal sepsis, serumcal protectin.*

INTRODUCTION

Neonatal sepsis is defined as a clinical syndrome of bacteremia with systemic signs and symptoms of infection in the first 4 weeks of life **(Bhale et al., 2016)**.

Neonatal sepsis is one of the most common causes of neonatal morbidity and mortality especially in preterms, low birth weight (LBW) babies. World Health Organization (WHO) estimates that 1 million deaths per year (10% of all under-five mortality) are due to NS and that 42% of these deaths occur in the 1st week of life **(Oza et al., 2014)**.

An early diagnosis of septicemia in that period is very crucial as the clinical course may be fulminating and life threating. The Blood culture is the golden standard test for neonatal sepsis; but the result is not available before 24- 48 hours and there are possible false negative responses in many instances **(Bhandari et al., 2014)**.

For such reason, a broad spectrum of inflammatory markers has been proposed for the diagnosis of neonatal sepsis. However, most of these markers are mediators of an acquired immunity response, which is largely immature in the neonatal period **(Labib et al., 2013)**.

On the contrary, innate immunity is fully developed in the first weeks of life, but no enough investigations evaluated the diagnostic power of innate immunity components **(Decembrino et al., 2015)**.

Calprotectin, a major product of innate immunity cell, is antimicrobial, calcium and zinc binding heterocomplex protein contained in the cytosol fraction of innate immunity cells and released immediately after host-pathogen interaction **(Stříž and Trebichavský, 2004)**.

For this it has been used as a nonspecific marker for activation of granulocytes and mononuclear phagocytes, in addition to protecting cells against micro-organisms, Calprotectin regulates adhesion of leukocytes to the endothelium and extracellular matrix during the inflammatory process.

Therefore, calprotectin has been proposed for the diagnosis of inflammatory conditions **(Abdel-Maaboud et al., 2012)**.

Aims of the Work

The main aim of this study is to evaluate the diagnostic power of serum calprotectin in neonatal sepsis.

PATIENTS AND METHODS

This prospective study was carried out in NICU of Bab El sheria university hospital, Al-azhar university and it was conducted on 30 neonates in the period from June 2018 to October 2019 they were divided into 2 groups:

Group 1 (proved sepsis, 15 cases): who had clinical features of sepsis and positive laboratory findings confirmed by positive blood culture.

Group 2 (Controls, 15 healthy neonates): who had age and sexmatched.

Inclusion criteria:

- Neonates between 1 day and 28 day.
- Neonates with suspected sepsis (poor activity, poor suckling, feeding intolerance, dehydration,.....).
- Neonates with positive sepsis workup (CBC, CRP, Blood culture,....).
- Neonates without any congenital anomalies.

Exclusion criteria:

- Neonates more than 28 days of age.
- Healthy neonates.
- Neonates with any congenital anomalies.
- Parents refuse to sign consent to be involved in the study.

Ethical consideration:

1. Approval from the ethical committees of both pediatric department and Faculty of Medicine Al-Azhar University.
2. Written consent for the study was obtained from the parents of these neonates participating in this study.
3. The data of the patients and the results of the study are confidential and the patients have the right to keep them.
4. The authors received no financial support for the study or the publication.
5. The authors declared that there is no conflict of interest regarding the study and publication.

Methods:

All patients will be subjected to the following:

- History taking (to detect risk factor for sepsis):
- Obstetric history (previous sibling death, previous admission to NICU, previous premature labour or low birth weight, etc).

- Prenatal history (Diabetes mellitus, maternal fever > 38, maternal UTI, maternal antibiotic etc.).
- Natal history (PROM >18h, maternal fever, prolonged 2nd stage of labour, etc).
- Postnatal history (low Apgar score at 1, 5 minutes, aggressive resuscitation, respiratory distress, cyanosis, fever, etc.).
- Present history which includes most common symptoms of sepsis.

Thorough clinical examination including:

General examination:

- Weight, length and skull circumference.
- Gestational age using last menstrual period date & new Ballard score **(Ballard et al., 1991)**.
- Vital signs (pulse-temperature-blood pressure-respiratory rate).
- □ Neonatal reflexes (Moro-grasping-suckling).

Local examination:

To detect sepsis clinical signs in the form of:

- Respiratory dysfunction: Apnea, intercostal retraction, increase oxygen requirement and signs of respiratory distress.
- Circulatory dysfunction: Poor peripheral circulation, hypotension, tachycardia, shock and prolonged capillary refill.
- GIT dysfunction: Abdominal distension, bloody stool, feeding intolerance, hepatomegaly and jaundice.
- Neurological dysfunction: Irritability, hypotonia, lethargy.

Investigation:

- Complete blood count (CBC) **(Rodwell et al., 1988)**.
- Quantitative C-reactive protein (CRP) **(Bhandari., 2014)**.
- Blood cultures **(Decamp et al., 2009)**.
- Serum Calprotectin level **(Decembrino et al., 2015)**.

Statistical analysis:

Data were analyzed using Statistical Program for Social Science (SPSS) version 15.0. Quantitative data were expressed as mean ± standard deviation (SD).

Qualitative data were expressed as frequency and percentage.

Mean (average): the central value of a discrete set of numbers, specifically the sum of values divided by the number of values.

Standard deviation (SD): is the measure of dispersion of a set of values. A low SD indicates that the values tend to be close to the mean of the set, while a high SD indicate that the values are spread out over a wider range.

RESULTS

Table (1): Comparison between studied groups as regard demographic data

Descriptive data Items		Patients (n = 15)	Control (n = 15)	P (Sig.)
Age at diagnosis (days) Mean ±SD		7.1 ± 1.5	8.0 ±1.2	0.08 NS
GA by LMP date (weeks) Mean ±SD		35.5 ± 2.4	36.9 ± 2.7	0.14 NS
Birth weight (kg) Mean ±SD		2.3 ± 0.5	2.7 ± 0.7	0.08 NS
Sex (n, %)	**Male**	9 (60%)	8 (53.3%)	0.71 NS
	Female	6 (40%)	7 (46.7%)	
Mode of delivery (n, %)	**C.S**	11 (73.3%)	9 (60%)	0.43 NS
	N.V.D	4 (26.7%)	6 (40%)	

This table shows no statistical significant difference (p-value < 0.05) between patients and control as regard demographic data.

Table (2): Description of Clinical manifestations in patients group

Clinical manifestation	n (%)	Clinical manifestation	n (%)
Respiratory distress	9 (47.3%)	**Hypoglycemia**	4 (26.7%)
Prolonged CRT	8 (53.3%)	**Hyperglycemia**	3 (20%)
Hypotonia	8 (53.3%)	**Bleeding**	3 (20%)
Jaundice	6 (40%)	**Tachycardia**	3 (20%)
Poor feeding	6 (40%)	**Bradycardia**	2 (13.3%)
Poor activity	8 (53.3%)	**Hypothermia**	6 (40%)
Hypotension	6 (40%)	**Hyperthermia**	2 (13.3%)
Abdominal distension	4 (26.7%)		

The most common clinical presentation for sepsis was respiratory distress,prolonged CRT, Hypotonia followed by poor feeding, poor activity, hypothermia, jaundice, hypotension, abdominal distension, hypoglycemia, Hyperglycemia, Bleeding, Tachycardia, Bradycardia, hyperthermia.

Table (3): Description of Laboratory data of the patients group at time of diagnosis

Laboratory data	Mean ± SD
TLC (X 10^3/mm^3)	17.8± 11.5
Total granulocytes (X 10^3/mm^3)	10.9 ± 9.9
Immature granulocytes (X 10^3/mm^3)	1.7± 1.3
I/T ratio	0.1844 ± 0.121
I/M ratio	0.284 ± 0.269
PLT (X 10^3/mm^3)	129.9 ± 138.5
Hb level (g/dl)	13.9± 4.2
Sepsis score	5.1± 1.8
CRP(mg/l)	35.3± 28.8
Serum Calprotectin(µic/ml)	5.8 ± 1.4

TLC: Total leukocytes count, **GRA:** granulocytes, **I/T:** immature/total **I/M:** immature/ mature, **Plts:** platelets, **Hb:** hemoglobin, **CRP:** c reactive protein

This table shows laboratory data in sepsis group as regard CBC parameters (TLC, total GRA, immature granulocytes, PLT, Hb level), Sepsis score, CRP and serum calprotectin level.

Table (4): Description of blood culture results in patients group

Blood culture results	No	%
No Growth	3	(20%)
Klebsiella	5	(33.3%)
Pseudomonas	2	(13.3%)
Acintobacter	2	(13.3%)
Staph	2	(13.3%)
E coli	1	(6.7%)

Blood cultures were withdrawn from all patients in this study.

As regards the organisms isolated from blood culture in sepsis group, Klebssiella was the

most common organism pseudomonas, Staph & E coli. followed by Acintobacter,

Table (5): Description of serum Calprotectin level in patients as regard blood culture results

Blood culture results	Serum Calprotectin	
	Mean	±SD
No Growth (n = 3)	3.4	1.7
Klebsiella (n = 5)	4.7	1.2
Pseudomonas (n = 2)	5.3	1.3
Acintobacter (n = 2)	4.5	0.9
Staph (n = 2)	3.9	1.5
E coli (n = 1)	4.3	

This table shows the highest level of S.calprotectin was presented in Pseudomonas then Klebsiella then Acintobacter.

Table (6): Comparison between studied groups as regards serum Calprotectin level

	Patients (n = 15)	Control (n = 15)	P (Sig.)
Serum Calprotectin (µic/ml) Mean ±SD	5.8 ± 1.4	1.3 ± 0.9	**< 0.001***

*: p-value < 0.001 is considered significant.

This table shows highly statistical significant difference (p-value < 0.001) between patients and control as regard serum calprotectin.

Table (7): Correlation between serum calprotectin level and clinical data in patients and control groups

	Patients group		Control group	
	r	P (Sig.)	R	P (Sig.)
GA (LMP date)	0.004	0.89 (NS)	0.21	0.3 (NS)
Birth weight	0.2	0.13 (NS)	0.45	0.23 (NS)
Age at assessment	0.07	0.67 (NS)	- 0.16	0.26 (NS)

GA: Gestational age, LMP: last menstrual period.
(r): Pearson correlation coefficient.

There was no statistical significant correlation between serum calprotectin level and clinical data in patients and control groups.

Table (8): Correlation between serum Calprotectin level and risk factors for neonatal sepsis in patients group

	(r)	P (Sig.)
Prematurity	0.066	0.51 (NS)
PROM	0.09	0.63 (NS)
Total parenteral nutrition	- 0.73	0.67 (NS)
Mechanical ventilation	1.8	0.76 (NS)
Central venous line	- 0.88	0.43 (NS)

(r): Pearson correlation coefficient.

There was no statistical significant correlation between serum calprotectin level and risk factors in patients group.

Table (9): Correlation between serum Calprotectin level and patients' hematological parameters

Serum Calprotectin	r	P	Sig.
TLC ($X10^3/mm^3$)	**0.292**	**0.034**	**S**
Total GRA ($X10^3/mm^3$)	0.284	0.061	NS
Immature GRA ($X10^3/mm^3$)	**0.425**	**0.002**	**S**
I/T ratio	**0.228**	**0.119**	NS
I/M ratio	**0.234**	**0.109**	NS
PLT Count ($X10^3/mm^3$)	0.034	0.92	NS
Blood culture	-2.409	0.016	**S**
Sepsis score	**0.704**	**< 0.001**	**HS**
CRP	-0.246	0.213	NS

(r): Pearson correlation coefficient.

This table shows:

There was highly significant positive correlation between serum calprotectin level and sepsis score in patients group.

There was significant positive correlation between serum calprotectin level, TLC, immature GRA and blood culture in patients group.

Other parameters showed non-significant correlation.

Table (10): ROC curve analysis showing the diagnostic performance of serum calprotectin(at diagnosis) discriminating septic neonates (patients) from control

Cut off	Area under the curve	Sensitivity	Specificity	PPV	NPV	p-value
2.25	0.992	100 %	97.5 %	98 %	100 %	< 0.001

The best cutoff serum calprotectin value for the diagnosis of neonatal sepsis was 2.25µic/mL (sensitivity 100%; specificity 97.5%; PPV 98%; NPV 100%).

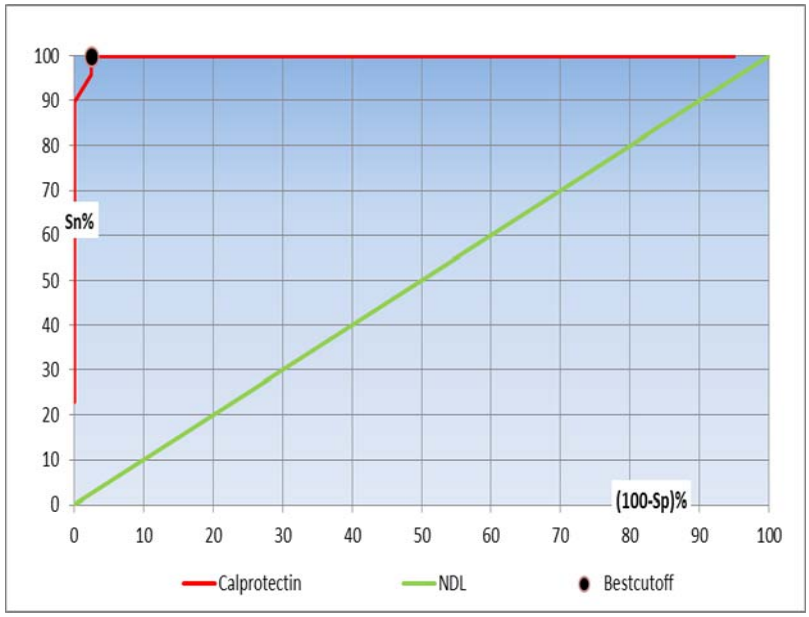

Figure (1): ROC curve analysis showing the diagnostic performance of serum calprotectin (at diagnosis) discriminating septic neonates (patients) from control

DISCUSSION

Despite the recent advances in neonatal care, sepsis remains a worldwide leading cause of morbidity, mortality and prolonged hospital stay in neonatal intensive care units, especially in developing countries. Sepsis accounts for 30- 50% of the total neonatal deaths in developing countries. About 20% of the neonates develop sepsis and approximately 1% dies due to

sepsis related causes **(Gandhi et al., 2013)**.

Diagnosis of neonatal septicemia remains a major challenge, as early signs of sepsis may be non-specific and the laboratory data are not fully reliable so that many studies have been ongoing to find predictors for neonatal sepsis that effectively identify patients who are at risk of infection **(Labib et al., 2013)**.

In the current study, a significant difference was reported between both groups regarding to abnormal total leucocytic count (leucocytosis or leucopenia), I: M ratio and platelets count (thrombocytopenia). This goes in agreement with the study of **Chiabi et al (2011)** which found that 76% of 216 neonates with sepsis had abnormal leucocytic counts and 66% had thrombocytopenia. This finding goes in contrast with the study of **Schelonka et al., (2005)** who stated that in the absence of clinical signs of sepsis, CBC values are unlikely to rule out infection.

Most patients 14 (93.3%) in our study had a positive CRP at the time of diagnosis ranging from 6 to 96 mg/L and CRP was significantly higher in septic group than other two groups). This finding goes in agreement with the study of **Terrin et al., (2011)**, who found that value of CRP was significantly different between septic and control groups. Also, the study of **Khassawneh et al., (2007)** revealed the same results as levels of CRP were significant higher in septic group. While this finding goes in contrast with the study of **Decembrino et al., (2015)**, in which he found no significance difference between studied groups as regards level of CRP.

In the current study, blood culture was positive in 12 (80%) neonates among the cases group. This finding goes in agreement with the study of **Terrin et al., (2011)** who found positive blood culture in 52(83.8%) neonates who were diagnosed as late onset sepsis.

In a previous Egyptian study, **El-Din et al., (2015)** investigated the epidemiology of neonatal sepsis and causative pathogens. The sepsis was proved in 140 (40.7%) cases by positive blood culture.

While **Rady et al., (2014)** found that the blood culture was positive in 19 (39.6%) among 48 neonates with LOS. **Abdel-Maaboud et al., (2012)** found positive blood culture in only 8 (16.6%) out of 48 neonates with suspected sepsis. Also

Decembrino et al., (2015) found positive blood culture in only 8 (19.51%) among 48 neonates. In another Indian study, **Gandhi et al., (2013)** investigated the incidence of neonatal sepsis among 238 neonates in a tertiary care hospital and found positive blood culture in 76 cases (32%).

This controversy in results may be due to differences in the environment, sample size of studied groups, different strategies and protocols of infection control in centers.

In the current study, Klebsiella was the most common organisms isolated from blood of sepsis followed by Acintobacter, pseudomonas, Staph & E coli.

This finding goes in agreement with **Decembrino et al., (2015)**, who revealed that Klebsiella was the most common isolated organisms.

Also this finding goes in agreement with the study of **Mohsen et al., (2017)** who investigated the emerging antimicrobial resistance in early and late-onset neonatal sepsis and found that Klebsiellapneumoniae (42%) was the most commonly isolated organism. Also, **Weston et al., (2011)** reported Group B Streptococcus was the most common isolated microorganism. Also this finding goes in agreement with the study of **Dzwonek et al., (2008)**, in which about 50% of the positive blood cultures yielded Klebsiellapneumoniae.

While this finding goes in contrast with the study of **El-Din et al., (2015)**, in which CoNS (74 isolates; 52.86%) was the most common isolated organism. Also our results are in contrast with the findings of other study **(Awad et al., 2016)**, in which E. coli was the main isolated pathogen (41.2%). Also this finding does not agree the study of **Afsharpaiman et al., (2012)**, in which the most commonly isolated pathogen was Enterobacterspp.

This controversy in results may be due to differences in the environment, infection control policy, sample size, the microbial etiology of sepsis and supportive care practice between centers among various geographical areas.

Serum level of calprotectin was significantly higher in septic group than control groups.

The ROC analysis of our data showed that the best cutoff serum calprotectin value for the diagnosis of neonatal sepsis was 2.25mic/mL (sensitivity 100%; specificity 97.5%; PPV 98%; NPV 100.

This finding is in agreement with **Decembrino et al., (2015)**, the optimal cut-o was 2.2 miμ/mL with sensitivity and specificity of 62.5% and 69.7% respectively.

In a previous similar study conducted in Egypt, **Abdel-Maaboud et al., (2012)** investigated the association between the calprotectin level and blood culture results, reporting that calprotectin level was significantly higher in the positive cultures. With nearly similar results, the optimal serum calprotectin cut-off value was (1.4 μg /dl), while Sensitivity, Specificity, PPV and NPV were 91.3 %, 94 %, 97.7 % and 87%, respectively.

In the study of **Terrin et al., (2011)** who investigated 83 neonates for suspected sepsis the optimal serum calprotectin cut off value was1.7mg/dl while Sensitivity, Specificity, PPV and NPV were 89 %, 96 %, 98 % and 80% respectively.

In the current study, Serum calprotectin was positively correlated with WBCs and IM ratio, this could be explained by the immediate release of calprotectin by innate immunity cells after host pathogen interaction. However, it was negatively correlated with lymphocytes and platelets. This goes in agreement with **Abdel-Maaboud et al., (2012)** who found that cases with positive blood cultures and/or poor outcomes had the highest levels of serum Calprotectin.

CONCLUSION

Serum Calprotectin levels of newborns are independent of gestational age and other clinical parameters. Calprotectin levels are significantly increased in infants with bacterial sepsis and might serve as an adjunctive diagnostic marker to allow prospective reduction of antibiotic use. The measurement could be useful in assisting clinical decisions about the management of neonatal sepsis.

RECOMMENDATIONS

Calprotectin is a promising early sensitive biomarker of neonatal sepsis for further investigations and studies.

Further large-scale studies from different Egyptian areas are warranted to standardize the best cut-off value for serum calprotectin.

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تقييم مادة كالبروتكتين فى مصل الدم كدليل تشخيصى فى الكشف المبكر لتسمم الدم لدى الأطفال حديثى الولادة

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التسمم الدموي البكتيري للأطفال حديثي الولادة هو عبارة عن عدوى للأطفال في الأربع أسابيع الأولى من العمر.

ومازال التسمم الدموي البكتيري يمثل سبباً هاماً من أمراض ووفيات الأطفال حديثي الولادة خاصة ناقصي النمو علي الرغم من توافر المضادات الحيوية.

ويعتبر الكالبروتكتين من أهم المنتجات الرئيسية للمناعة الفطرية وهو مضاد للميكروبات ويحمي الخلية من الميكروبات وينظم التصاق كرات الدم البيضاء بالخلايا لحمايتها أثناء عملية الالتهاب ويتم إفراز الكالبروتكتين من خلايا المناعة الفطرية على الفور بعد تعرض الجسم للميكروبات. ولقد تم استخدام الكالبروتكتين لتشخيص العديد من الأمراض الإلتهابية ولكن استخدامه في تشخيص حالات التسمم الدموي بالأطفال حديثي الولادة لم يتضح حتى الآن.

والغرض من هذا البحث هو التحقق من قدرة الكالبروتكتين على تشخيص التسمم الدموي في الأطفال حديثي الولادة.

وقد أجري هذا البحث في وحدة العناية المركزة للأطفال حديثي الولادة بمستشفي السيد جلال الجامعي و مستشفى الحسين الجامعي وقد اشتمل هذا البحث علي 30 طفلاً حديثي الولادة وناقصي النمو وذلك في الفترة من يونيو 2018 وحتى أكتوبر 2019.

وتم تقسيم الأطفال في تلك الدراسة إلى 2 مجموعات:

1. المجموعة الأولى (15 حالة) وهم الأطفال الذين ظهرت عليهم أعراض التسمم الدموي وتم التأكد من إصابتهم عن طريق الأبحاث المعملية.

2. المجموعة الثانية (15 حالة) وهم اطفال اصحاء للمقارنة.

وقد خضع كل طفل في هذه الدراسة لعمل الآتي:

1. أخذ التاريخ المرضي قبل وأثناء وبعد الولادة.

2. الفحص الإكلينيكي الشامل.

3. ملاحظة العلامات الخاصة بوجود الميكروب في الدم في صورة:

ولكل الحالات تم عمل التحاليل الآتية :

1. صورة دم كاملة مع التركيز علي نسب وعدد خلايا النيتروفيل الناضجة والغير ناضجة.

2. قيمة بروتين سي التفاعلي.

3. مزرعة دم.

4. قياس نسبة الكالبروتكتين بالدم عن طريق قياس مستوى مصل الكالبروتيكتين كميا بواسطة انزيم مرتبط المناعي مقايسة مع الأجسام المضاده وحيدة النسبه ضد كالبروتيكتين الإنسان (تم شراؤها من Kit, SunRed, Shanghai, China).

وكانت نتائج دراستنا:

1. نسبة التسمم الدموي في الأطفال حديثي الولادة لا تتأثر بالجنس،العمر.

2. مستوى مصل الكالبروتيكتين يزداد في حالات التسمم الدموي البكتيري للأطفال حديثي الولادة.

3. هناك علاقه طرديه بين ارتفاع نسبة الكالبروتيكتين وبين ارتفاع عدد كرات الدم البيضاء، سي آر بي، معدل رودويل، نسبة الآي تي والآي إم، مزارع الدم الإيجابية والحالات المتوفية.

4. أفضل قيمة مصل الكالبروتيكتين لتشخيص الإنتان الوليدي هو 2.25 ميكرو/ مل بحساسية 100% وخصوصية 97.5%.

الإستنتاج:

بناءا على النتائج التي تم جمعها وتحليلها إحصائيا وجد أن مستوى الكالبروتكتين في مصل دم الأطفال حديثي الولادة مرتفع في المجموعة المصابة بالتسمم الدموي عن المجموعة الضابطة.

لذلك نستطيع أن نقرر أن نسبة الكالبروتكتين في مصل الدم تعتبر كاشف دقيق لمرض التسمم الدموي في حديثي الولادة. وأن مستويات الكالبروتيكتين تزداد بشكل كبير عند الرضع مع التسمم الدموي، وربما تكون بمثابة علامة تشخيصية مساعدة للحد من استخدام المضادات الحيوية، ومفيدة في اتخاذ القرارات السريرية المساعدة لتشخيص وعلاج التسمم الدموي للأطفال حديثي الولادة.

التوجيهات:

على ضوء نتائج دراستنا نستطيع أن نوصي بأن:

1. نستطيع استخدام مستوى الكالبروتيكتين في مصل دم الأطفال حديثي الولادة ناقصي النمو في التشخيص المبكر للتسمم الدموي لأنه يمتلك حساسية عالية (100%) وخصوصية عالي (97.5%).

2. نستطيع استخدام مستوى الكالبروتيكتين في مصل دم الأطفال حديثي الولادة كأداة للتنبؤ بمآل حالات التسمم الدموي للأطفال حديثي الولادة ناقصي النمو.