EVALUATION OF MELATONIN EFFECT AS ADJUVANT THERAPY IN TREATMENT OF SEPTIC NEWBORNS

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ABSTRACT

Background: *Neonatal sepsis is a clinical syndrome with a systemic sign and symptom of infection in the first 4 weeks of Life, sepsis is an important cause of morbidity and mortality, Free radical and reactive oxygen species ROS play An important role in the pathogenesis of neonatal sepsis, Melatonin is an endogenous substance produced from the pineal gland, Melatonin is a highly effective antioxidant and free radical scavenger.*

Aim of work: *Evaluate the therapeutic efficacy of melatonin in the treatment of neonatal sepsis as adjuvant therapy.*

Design: *A prospective case-control study that was carried out on 40 neonates with neonatal sepsis diagnosed clinically and laboratory, they were Enrolled from NICU of Bab-alsha'reya university hospital in the period from April 2019 to October 2019.*

Patient and method: *The Study included 40 neonates, divided by systemic random method into two groups,**(Group 1)** 20 neonates with sepsis received a single oral dose of melatonin in a dose of(20mg/day)as a single dose ,**(Group2)** 20 neonates with sepsis didn't receive melatonin, both groups received the same protocol of antibiotics of the unit, investigations were done included CBC and CRP before administration of melatonin and 48h after administration of melatonin in group 1, in group 2 CBC, CRP at 48h after administration of antibiotics.*

Inclusion criteria: *Any term or preterm with neonatal sepsis diagnosed clinically and laboratory, their weight less than 4kg.*

Exclusion criteria: *Hypoxic-ischemic encephalopathy (HIE), major congenital anomalies, Persistent vomiting, and septic shock.*

Results: *The study showed that serum parameter including (TLC, ANC, I/T ratio, platelets, and CRP) were similar in both group before administration of melatonin in group 1, while there was a significant difference in serum parameters, after 48h of starting administration of melatonin, so the present study showed that melatonin improves serum parameters and improve the clinical course of septic newborns.*

Conclusion: *The administration of melatonin as adjuvant therapy in the treatment of neonatal sepsis is associated with better prognosis and improves outcomes.*

Keywords: *Neonatal sepsis, Evaluation, Melatonin, Adjuvant therapy.*

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. When pathogenic bacteria gain access into bloodstream, they may cause overwhelming infection without much localization (septicemia) or may get predominantly localized to the lung (pneumonia) or the meninges (meningitis) **(Weimer et al., 2020)**.

Neonatal sepsis is an important cause of morbidity and mortality despite the major advance in management **(Alvis-Guzmán et al., 2019)**.

Oxidative stress is defined as the tissue damage resulting from an imbalance between an excessive generation of oxidant compounds and insufficient antioxidant defense mechanisms **(Colombo et al., 2017)**.

Melatonin, (N-acetyl-5-methoxytryptamine) that is synthesized and secreted from the pineal body, is highly effective antioxidant, free radical scavenger, and a primary circadian regulator **(Mahmood et al., 2019)**.

Melatonin has important antioxidant properties owing to direct and indirect effects. It directly scavenges reactive oxygen and reactive nitrogen species, prevents molecular oxidation, improves mitochondrial physiology and biogenesis. Its indirect antioxidant effects stem from its ability to stimulate the activities of the anti-oxidative enzymes, such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase **(Chahbouni et al., 2017)**.

Aims of the Work

To evaluate the therapeutic efficacy of melatonin in the treatment of neonatal sepsis as adjuvant therapy.

PATIENTS AND METHODS

This study was a prospective case-control study and was conducted on 40 neonates with neonatal sepsis on the basis of both clinical and laboratory criteria. They were enrolled from the NICU of Bab AL-sha'reya University Hospital. Cases were selected during the study period from April 2019 to October 2019

and were divided by systemic random method into two groups.

Group I:

Twenty (20) neonates with sepsis receiving a single oral dose of melatonin in a dose of 20mg/day. This group received also antibiotics according to the standard protocol of the unit.

Group 2:

Twenty (20) neonates with sepsis not receiving melatonin as control group. This group receives antibiotics according to the same protocol.

So, the two groups were given antibiotics according to the standard protocol (Ampicillin plus Gentamycin).

Melatonin was given 4 tablets (20mg/day) as a single dose dissolved in distilled water and given through the Ryle as a single dose **(Colella et al., 2016)**.

Inclusion criteria:

a. Any full-term or preterm with neonatal sepsis diagnosed clinicaly and laboratory.

b. Gestational age: between 32weeks and 39 weeks according to the new Ballard score **(Singhal et al., 2017)**.

Exclusion criteria:

1. Major congenital anomalies e.g (GIT anomalies).
2. Persistent vomiting.
3. Neonates with hypoxic-ischemic encephalopathy (HIE), intracranial hemorrhage, and respiratory distress syndrome (RDS).

Criteria employed for defining the sepsis score:

- **High probable sepsis (HPS):**

a. At least 3 sepsis-related clinical criteria.

b. CRP more than5 mg/ml.

c. At least 2 other altered serum parameters.

d. Blood culture: positive or negative.

- **Probable sepsis (PRS):**

a. At least 3 sepsis-related clinical criteria.

b. CRP more than5 mg/ml.

c. At least 2 other altered serum parameters.

d. Blood culture: negative.

- **Possible sepsis (POS):**

a. At least 3 sepsis-related clinical.

b. CRP less than5 mg/ml.

c. Less than 2 other altered serum parameters.

d. Blood culture: negative.

Ethical consideration:

1. A written informed consent was obtained from their legal guardians.
2. An approval by the local ethical committee was obtained before the study.
3. The researchers declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
4. All data of the study are confidential.

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All cases were subjected to the following:

A. Careful history taking:

Prenatal, natal and postnatal history taking that included:

1. Intrapartum fever >38oC.
2. Antepartum hemorrhage.
3. Premature rupture of membranes > 18 hours.
4. Difficult labor.
5. Mode of delivery.
6. Twins.

B. Clinical Examination:

1. Age in days.
2. Determination of gestational age.
3. Assessment of Anthropometric measurements: weight, length, head circumference and abdominal circumference.
4. Clinical evidence of neonatal sepsis as:

- Lethargy.
- Poor Moro and suckling reflexes.
- Temperature instability.
- Respiratory distress- apnea.
- Tachycardia, bradycardia, poor perfusion.
- Gastrointestinal manifestations (vomiting-diarrhea- abdominal distension- hepatosplenomegaly).
- Colours (jaundice-cyanosis-pallor).
- Bleeding tendency.
- Convulsions-hypotonia.
- Umbilical sepsis.
- Skin mottling.
- Scleredema.

C. Laboratory Investigations

a. Group 1:

Complete blood count (CBC) done by (sysmex xp 300) and CRP done by (cobas 311) before melatonin and antibiotics and 48 hours after administration of melatonin and antibiotics of the standard protocol of the unit.

b. Group 2:

Complete blood count (CBC) has done by sysmex xp 300, and CRP done by cobas 311 before antibiotics and 48 hours after antibiotics of the standard protocol only.

Statistics:

The statistical analysis was performed using SPSS for Windows, version 20. Data were expressed as a range and mean± standard deviation (SD). Differences between groups in continuous variables were tested for significance with paired t-test while univariate analysis was done with the Chi-square test. For all statistical tests done, P value< 0.05 was considered significant.

RESULTS

Table (1): Comparison between G1 and G2 as regard of demographic characteristic

	Gestational Age (Weeks)		Weight (kg)			Mode of delivery		Sex	
	Range	Mean± STD	Range	Mean ± STD		NVD	CS	Male	Female
Group1 N=20	32-39	36.5± 1.02	1.7-4.2	2.84± 0.47	No	10	10	12	8
					Percentage (%)	50	50	60	40
Group2 N=20	32-39	36.1± 2.8	1.7-4.2	3.29± 0.99	No	9	11	10	10
					Percentage (%)	45	55	50	50
t. test	0.194		0.7121		Y^2	0		0	
P. value	0.839		0.519		P. value	1		1	

Table (1) shows no statistical significant difference between G1 and G2 as regards gestational age (weeks), weight in (kg), mode of delivery and sex ($p>0.05$).

Table (2): Comparison between G1 and G2 as regard type of sepsis

		Type of sepsis	
		Early onset	**Late onset**
Group1 N=20	**No**	12	8
	Percentage (%)	60	40
Group2 N=20	**No**	9	11
	Percentage (%)	45	55
Y^2		0.074	
P. value		0.729	

Table (2) shows no statistically significant difference between G1 and G2 as regards type of sepsis ($p>0.05$).

Table (3): Comparison between G1 and G2 as regards sepsis score

Sepsis score		**Before**	**After 48h**		
		High probable	**Possible**	**Probable**	**High probable**
Group1 N=20	**No**	20	7	13	0
	Percentage (%)	100	35	65	0
Group2 N=20	**No**	20	0	16	4
	Percentage (%)	100	0	80	20
Y^2		0	9.95		
P. value		1	0.006*		

Table (3) shows that there was no significant difference in sepsis score between G1 and G2 before starting melatonin, while there was significant improvement after 48 hours in both groups with more improvement of sepsis score in G1 than G2.

Table (4): Comparison between G1 and G2 as regards Hs-CRP

Hs CRP	**Before**		**After 48h**		**Before&48H**
	Range	**Mean±STD**	**Range**	**Mean±STD**	**P. value**
Group1 N=20	24-96	50.03±21.9	4.2-24	10.9±4.95	0.0031*
Group2 N=20	24-96	51.1±14.7	12-48	22.8±9.09	0.0019*
t. test	0.131		5.415		
P. value	0.865		0.002*		

Table (4) shows that there was no significant difference in hs CRP between G1 and G2 before starting melatonin, while there was significant decrease of Hs-CRP after 48 hours towards the normal range in both groups with more decrease in Hs-CRP in G1 than G2.

Table (5): Comparison between G1 and G2 as regard total leucocytic count (TLC)

	Before		After 48h		Before& 48H
	Range	Mean±STD	Range	Mean±STD	P. value
Group1 N=20	12-23	15.7±3.17	4.9-18.4	10.1±4.26	0.0062*
Group2 N=20	16.4-28	21.55±4.12	7.2-25	15.33±4.89	0.022*
t. test	0.695		9.323		
P. value	0.431		0.0032*		

Table (5) shows that there was no significant difference in TLC between G1 and G2 before starting melatonin, while there was significant decrease of TLC after 48 hours towards the normal range in both groups with more decrease in G1 than G2.

Table (6): Comparison between G1 and G2 as regard absolute neutrophil count (ANC)

ANC	Before		After 48h		Before&48H
	Range	Mean±STD	Range	Mean±STD	P. value
Group1 N=20	5.7-19.7	9.85±2.77	1.9-7.3	3.53±1.39	0.0041*
Group2 N=20	5.9-21.1	12. 34±4.81	1.9-16	8.89±2.44	0.013*
t. test	0.392		7.134		
P. value	0.712		0.0029*		

Table (6) shows that there was no significant difference in ANC between G1 and G2 before starting melatonin, while there was significant decrease in ANC after 48 hours of starting melatonin towards the normal range in both groups with more decrease in G1 than G2.

Table (7): Comparison between G1 and G2 as regard platelet (PLT)

PLT	Before		After 48h		Before&48H
	Range	Mean+STD	Range	Mean+STD	P. value
Group1 N=20	48-177	156.1±39.74	90-280	129.9±63.41	0.0171*
Group2 N=20	37-159	101.8±42.1	90-196	141.8±54.68	0.029*
t. test	0.412		0.154		
P. value	0.691		0.910		

Table (7) shows that there was no significant difference in PLT count between G1 and G2 before starting melatonin, while there was significant increase in PLT count after 48 hours towards the normal range with more increase in G1 than G2.

Table (8): Comparison between G1 and G2 as regard immature/ total (I/T) ratio

I/T		Before	After 48h
		>20%	>20%
Group1 N=20	No	20	8
	Percentage (%)	100	40
Group2 N=20	No	20	11
	Percentage (%)	100	55
Y^2		0	3.012
P. value		1	0.019*

Table (8) shows that there was no significant difference in I/T ratio between G1 and G2 before starting melatonin, while there was significant improvement in I/T ratio after 48 hours (I/T ratio less than 20%) with more improvement in G1 than G2.

Table (9): Comparison between G1 and G2 as regard outcome

		Fate	
		Living	Death
Group1 N=20	No	16	4
	Percentage (%)	80	20
Group2 N=20	No	15	5
	Percentage (%)	75	25
Y^2		3.231	
P. value		0.091	

Table (9) shows no statistical significant difference between G1 and G2 as regards Fate ($p<0.05$).

DISCUSSION

Neonatal sepsis remains a major clinical problem in neonatology, with high morbidity and mortality rates despite the progress in neonatal intensive care and antibiotics. The host defense against infections is immature in the newborn infant, and this makes the neonate more susceptible to intensive infection **(Kim, 2018)**.

The early signs and symptoms are nonspecific and cannot be differentiated from noninfectious disorders, so preventable mortality might increase if the treatment is delayed until the infection is well established **(Chauhan, 2017)**.

When septic infection occurs, microorganisms invade the bloodstream and release various substances that in turn activate the endogenous mediators of the host systemic response. Sepsis may present with only mild systemic symptoms or progress to septic shock and/or multiple organ failure, which are associated with a mortality rate of 50% or greater **(Colella et al., 2016)**.

Oxidative stress and oxygen free radicals (OFR) have been correlated with sepsis severity and sepsis-induced morbidity **(Jang et al., 2017)**.

The therapy administered in the initial "golden hours" in severe sepsis is likely to influence the outcome. Effective therapies can improve the outcome of sepsis **(Rhodes et al., 2017)**. Several clinical studies that used melatonin showed that it reduces oxidative stress in newborns with sepsis where there is excessive inflammatory reaction and ROS/RNS production **(Gonzalez-Candia et al., 2019)**.

Melatonin (MT), a hormone secreted by the pineal gland in the brain, has been shown to function as a direct free radical scavenger and an indirect antioxidant via its stimulatory actions on anti-oxidative enzymes **(Arnao et al., 2019)**.

This study included neonates with sepsis which can be classified into high probable sepsis (HPS) or probable sepsis (PRS) or possible sepsis (POS) or no sepsis (NS) according to criteria employed for defining the sepsis score **(Colella et al., 2016**; **Eschborn et al., 2019)**.

The present study found that there was no significant difference between both groups as regard the mode of delivery. This was in agreement with **Perrone et al., (2018)** and **Eschborn et al., (2019)**. This was disagreed with **Puopolo et al., (2017)** who was observed that babies born by vaginal delivery were more likely to have EOS than those delivered

by caesarean section. **Das et al., (1998)** mentioned that infants delivered by CS were less likely to develop septicemia. This may be related to good sterilization and intrapartum chemoprophylaxis which dramatically decrease incidence of sepsis in neonates delivered vaginaly.

In this study, it was found that was no significant difference between both groups as regard sex. The sex was not significantly associated with increased frequency of sepsis. This was in agreement with the study of **El-Behedy et al., (2019)** and also with the study of **Betty and Inderpreet, (2005)** that had conducted his study on 1743 newborns and found that the rates of infection were similar in males and females. This was in disagreement with **Walkovich (2016)** who was found that the frequency of neonatal sepsis was significantly higher in males. The difference in the results may be related to racial or genetic differences between populations.

The present study showed that melatonin would improve serum inflammatory parameters and improved the clinical course of septic newborns as judged by Criteria employed for defining the sepsis score. This was in agreement with **Colella et al., (2001)** that was found that melatonin have anti-inflammatory effect.

The present study found that there was no significant difference in Hs-CRP between G1 and G2 before starting melatonin, while there was a significant decrease of Hs-CRP after 48 hours towards the normal range in both groups with more decrease in G1 than G2 **Colella et al., (2001)**.

In this study TLC and the ANC were significantly higher in both groups of septic newborns this was in agreement with **El-Sonbaty et al., (2016)** and **Abd Allah et al., (2017)** who mentioned in their study that, TLC and the ANC were significantly higher in septic newborns.

This study found that there was no significant difference in TLC and the ANC between G1 and G2 before starting melatonin, while there was decrease in TLC and the ANC after 48 hours in both groups towards the normal range with more decrease in G1 than G2 **Colella et al., (2001)**.

This study found that I/T ratio higher than 0.2 in both groups. This was in agreement with **Chen, (2019)**; **Mulkey (2001)** who reported that I/T ratio a ratio higher than 0.2 in their septic newborns.

This study found that there was no significant difference in I/T ratio between G1 and G2 before starting melatonin, while there was improvement in I/T ratio after 48 hours in both groups (I/T ratio less than 20%) with more improvement in G1 than G2.

This study found that there was no significant difference in platelet count between G1 and G2 before starting melatonin, while there was a significant increase in platelet count after 48 hours towards the normal range in both groups with more increase in platelet count in G1 than G2, this was in agreement with **Colella et al., (2001)**.

So there was an improvement in sepsis score in both groups with more significant improvement in group 1 than group 2 and this was in agreement with **Colella et al., (2001)**. Administration of melatonin as adjuvant therapy in the treatment of neonatal sepsis is associated with improvement of clinical outcome of septic newborns as melatonin improves serum inflammatory parameters **(Gonzalez-Candia et al., 2019)**.

CONCLUSION

Based on the results of this study we concluded that:

1. Melatonin improves the clinical outcome of neonatal sepsis.
2. Administration of melatonin as adjuvant therapy in the treatment of neonatal sepsis is associated with better prognosis and improves outcomes.

RECOMMENDATIONS

Based on the results of this study we recommend the following:

1. Oral administration of melatonin is recommended as adjuvant therapy besides the antibiotics in the treatment of neonatal sepsis.
2. More studies should be done with different doses of melatonin to be used in the treatment of neonatal sepsis
3. More studies should be done to use melatonin in neonatal disorders characterized by excessive inflammatory reaction as Hypoxic ischaemic encephalopathy (HIE), Respiratory distress syndrome (RDS), and Bronchopulmonary dysplasia (BPD).

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استخدام الميلاتونين كعلاج مساعد في علاج التسمم الدموي الوليدي

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مقدمة البحث: التسمم الوليدي هو أحد أهم أسباب الاعتلال والوفيات على الرغم من تقدم كبير في الرعاية المركزة لحديثي الولادة والمضادات الحيوية.

الميلاتونين هو الهرمون الرئيسي يفرز من الغدة الصنوبرية.

الميلاتونين يعمل عن طريق التبرع بالإلكترون لإزالة سموم جزيئات الأكسجين التفاعلية مثل الهيدروكسيل شديدة السمية وكذلك بيروكسيد الهيدروجين.

وبجانب هذا التأثير الميلاتونين يقوم بتحفيز إنزيمات مضادات الأكسدة.

الهدف من البحث: تقييم أثر الميلاتونين في علاج التسمم الدموي عند الأطفال حديثى الولاده.

مواد وطرق البحث: تم إجراء هذا البحث بوحدة العناية المركزة للأطفال حديثي الولادة في مستشفى باب الشعرية بجامعة الازهر وتم اختيار عدد (40) مصاب بمرض التسمم الدموي تم تقسيمه إلى مجموعتين.

- **مجموعة (1):** (20) طفل مصاب بالتسمم الدموي يتناول الميلاتونين كجرعة واحده 20 مجم.

- **مجموعة (2):** (20) طفل مصاب بالتسمم الدموي لا يتناول الميلاتونين كمجموعه تحكم.

- كلا المجموعتين يتناولوا المضادات الحيويه التقليديه.

مجموعه 1 ومجموعه 2 يتناولون مضادات حيوية تقليديه.

ستخضع جميع الحالات على ما يلي:

- التاريخ المرضي كامل.

- الفحص الإكلينيكي الشامل.

الأبحاث وتتضمن:

- في المجموعة الأولى صوره دم كاملة وبروتين سى التفاعلى قبل إعطاء الميلاتونين وبعد 48 ساعة من إعطاء الميلاتونين وهذه المجموعة تتناول أيضا المضاد الحيوى التقليدي.

- فى المجموعة الثانية يتم قياس صوره دم كاملة وبروتين سى التفاعلى بعد 48 ساعة من إعطاء المضاد الحيوى التقليدى فقط.

نتائج البحث: في هذه الدراسة لم تظهر أي فروق ذات دلالة إحصائية بين المجموعتين فيما يتعلق بالجنس وطريقة الولادة.

أظهرت الدراسة الحالية أن تمزق الغشاء الأمنيوسي السابق لأوانه لمده أكثر من 18 ساعة هو العامل الأكثر شيوعا للتسمم الوليدي.

في الدراسة الحالية (صوره الدم وبروتين سي التفاعلى عالى الحساسية) كانت مماثلة في المجموعتين على حد سواء في هذه الدراسة قبل إعطاء الميلاتونين.

هناك انخفاض في كلا المجموعتين نحو المعدل الطبيعي في بروتين سي التفاعلى عالى الحساسية بعد 48 ساعة ولكن المجموعة الأولى أكثر انخفاضا من المجموعة الثانية.

هناك انخفاض في كلا المجموعتين في كرات الدم البيضاء نحو المعدل الطبيعي بعد 48 ساعة ولكن المجموعة الأولى أكثر انخفاضا من المجموعة الثانية.

هناك انخفاض في كلا المجموعتين في عدد النيتروفيل نحو المعدل الطبيعي بعد 48 ساعة ولكن المجموعة الأولى أكثر انخفاضا وتحسنا من المجموعة الثانية.

هناك تحسن في كلا المجموعتين في نسبه الخلايا الغير ناضجة إلى نسبه الخلايا الكلية الى اقل من 20٪ بعد 48 ساعة ولكن المجموعة الأولى أكثر تحسنا من المجموعة الثانية.

هنـــاك زيـــادة فـــي كـــلا المجمـــوعتين فـــى عـــدد الصـــفائح الدمويـــة نحـــو المعـــدل الطبيعـــى بعـــد 48 ســـاعة ولكـــن المجموعـــة الأولى أكثر زيادة وتحسنا من المجموعة الثانية.

الإستنتاج: استناداً إلى نتائج دراستنا ونحن نخلص إلى أن:

- الميلاتـــونيين لـــه دور فـــى فـــى تحســـبن الحالـــه الصـــحيه للـــذين يعـــانون مـــن التســـمم الـــدموى الوليـــدى مقارنـــه بقيـــاس المـــواد المسببة للالتهاب والتسمم الدموى فى الدم.

- إعطـــاء الميلاتـــونين كعـــلاج مســـاعد فـــى عـــلاج التســـمم الـــدموى مرتبط بتحسين النتائج وخفض تكاليف الرعاية الصحية.

توصيات البحث: استناداً إلى نتائج دراستنا نوصي بالتالى:

- ينصـــح تنـــاول الميلاتـــونين كعـــلاج مســـاعد بجانـــب المضـــادات الحيوية في علاج التسمم الدموى الوليدى.

- ونوصـــى بعمـــل ابحـــاث لاســـتخدام الميلاتـــونين فـــي امـــراض الأطفـــال حـــديثي الـــولادة والتـــى تتميـــز بتفاعـــل التهـــابى مفـــرط مثـــل المصـــابين بـــاعتلال المـــخ الاختنـــاقى ومتلازمـــة الضـــائقة التنفسية وخلل التنسج القصبي الرئوى.