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Role of Melatonin in Treatment of Necrotizing Enterocolitis in Preterm Neonates

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Abstract

Background: Necrotizing enterocolitis (NEC) is one of the most dangerous gastrointestinal diseases that affects the neonates especially preterm neonates. It can lead to severe morbidity and even mortality, so early detection of NEC would give us good chance for early prevention and treatment with better prognosis. Free radicals play a significant role in the pathogenesis of neonatal sepsis and NEC. It has been suggested that melatoninas an antioxidant can be used to counteract the toxicity of oxygen radicals that are released during neonatal illness.

Aim of Study: Is to Determine the role of melatonin as an adjuvant therapy in treating necrotizing enterocolitis (NEC) in preterm neonates.

Patients and Methods: A prospective clinical trial study was conducted on 20 preterm neonates which suffer from NEC diagnosed on the basis of both clinical and laboratory criteria. group (G I) (n=10) received melatonin and antibiotics, while the control group (G II) (n=10) was treated with antibiotics only. Melatonin was administered as 20 mg for 3 consecutive days and antibiotics were administered according to a standard protocol protocol and followed-up of symptoms and signs of NEC after 5,10 and 15 days of starting treatment.

Results: As regard outcome of NEC, In group I there were 9 (90%) cases improved and 1 (10%) case not improved but In group II there were 5 (50%) cases improved and 5 (50%) cases not improved, so more cases in group I who received melatonin showed improvement of NEC than group II. As regard mortality, one baby (10%) died and 9 (90%) survived in group I compared to 3 babies (30%) died and 7 babies (70%) survived in group II.As regard length of NICU stay the patients who received melatonin (group I) stay for a shorter period in NICU compared to group II who received traditional therapy only.

Conclusion: Melatonin administration as an adjuvant therapy in NEC treatment in preterm neonates is associated with improvement of clinical and laboratory outcome.

Key Words: *Preterm neonates – Necrotizing enterocolitis – Melatonin.*

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Introduction

NECROTIZING enterocolitis (NEC) is one of commonest gastrointestinal surgical emergency in premature infants less than 37 weeks and less than 1.500gm [1]. Preterm neonates are more susceptable to Oxidative Stress (OS) damage than full term infants due to prematurity of organs, rapidly increasing energy demand, production of excessive Reactive oxidative stress (ROS) and the deficiency of antioxidant systems that come to maturity later [2].

Necrotizing enterocolitis is an inflammatory disease of gastrointestinal tract, present with multifactorial etiology [3]. Oxidative stress and exaggerated inflammatory response in the premature Gut, abnormal intestinal bacterial colonization play a role in pathogenesis of NEC, prematurity, enteral feeding, hypoxia and intestinal ischemia are also involved in the pathogenesis of the disease [4].

The combination of immature antioxidant defense system and elevated levels of ROS place the neonate in high risk of intestinal damage, but this injury can be improved by using radical scavenger [4].

Melatonin is a highly and free radical scavenger [5].It has many physiological functions in circadian rhythm, sleep neuroendocrine, and cerebrovascular systems [6]. Melatonin also has important role as an antioxidant, anti-inflammatory and anti-apoptotic agent [7,8].

Melatonin has been to be effective in reducing molecular damage, tissue loss and improving physiologic outcome as chronic lung disease, perinatal brain injury, NEC and sepsis [9]. Effects of melatonin in preventing gastrointestinal disturbances

were studied in rat [10]. Studies demonstrates that TNF-ct and IL28 were decreased in animal model after NEC and treated with melatonin [10]. So it is possible that antioxidant melatonin might be useful in management of neonate with NEC.

Aim of the work:

Is to evaluate the role of melatonin in treatment of necrotizing enterocolitis in preterm neonates.

Patients and Methods

This study was carried out on 20 preterm neonates suffering from NEC and conducted at NICU in Tanta University Hospital during the period from January 2017 to December 2017. Patients were subdivided in two groups:

- *Group (I):* Included 10 preterm neonates who received antibiotics as standard protocol and oral melatonin 20mg/day once.
- *Group (II):* Included 10 preterm neonates who received antibiotics only as standard protocol.

All patients were subjected to:

A- Full history taking and thorough clinical examination

B- Investigations: Complete blood count, renal functions, liver functions, C reactive protein (CRP), capillary blood gases, serum electrolytes (Na, K, Ca, Mg).

C- Radiological investigations: Pelvi-abdominal US, X-ray abdomen and pelvis.

D- Melatonin was administrated as 20mg for 3 consecutive days, antibiotics were given according to a standard protocol and followed-up of symptoms and signs of NEC after 5, 10 and 15 days of starting treatment in addition to followed-up by laboratory investigations.

Results

This study was carried out on 20 preterm neonates with NEC.

Table (1) showed there was non significant difference regarding gender, gestational age and weight between both groups.

Fig. (1) showed all cases in patients and controls (100%) presented by increase abdominal girth and there was no significant difference before starting treatment. Significant difference of abdominal circumference between both groups on D5, D10 and D15. Significant difference in both groups at D5, D10 and D15 on comparison between before and after receiving treatment.

Fig. (2) showed all (100%) cases in group I and group II presented by feeding residual. After starting treatment we noticed that, Significant improvement as regard feeding residual in both groups on comparison between before and after receiving treatment on D15 only. Significant improvement as regard feeding residual in D5, D10 and D15 in group I who received melatonin on comparison to D10 and D15 in group II who received traditional treatment.

Fig. (3) showed six (60%) cases of group I and group II presented by thrombocytopenia before starting treatment. After starting treatment there was significant improvement of thrombocytopenia to reach to normal platelets count in group I who received melatonin than group II who received traditional treatment. Significant difference in both groups at D15 in comparison between before with D5, D10 and D15 in each group.

Fig. (4) showed on comparison before and after treatment in each group we found that Significant improvement of serum bicarbonate level as returned to normal values in patients who received melatonin (group I) treatment on D1 0 and D1 5 while significant improvement of group II at D10 only.

Fig. (5) showed six (60%) cases of groupI and eight (80%) cases of group II presented with hyponatremia before starting treatment.

After starting treatment, on comparison between both groups significant difference at D10 and D15. On comparison before and after treatment in each group we found that more Significant improvement of hyponatremia in patients who received melatonin treatment (group I) on D1 0 and D1 5 while significant improvement of group II at D15 only.

Fig. (6) showed significant difference as the patients who received melatonin (group I) stay for a shorter period in NICU compared to group II who received traditional therapy only.

Fig. (7) showed in group I there were 90% of cases improved and 10% of cases not improved but in group II there were 50% of cases improved and 50% of cases not improved. Significantly more cases in group I who received melatonin showed improvement of NEC than group II who received only traditional treatment.

Table (1): Demographic data (gender, gestational age and weight) of the studied groups.

	Groups		Chi-Square or *t*-test	
	Group I (n=10)	Group II (n=10)	X^2 or *t*	*p*-value
Gender:				
Male	5 50.00	2 20.00	1.978	0.160
Female	5 50.00	8 80.00		
Gestational age (Week):				
Range	30–33	27–34	0.675	0.509
Mean ±SD	31.800± 1.229	31.200± 2.530		
Weight (kg):			1.656	0.115
Range	1.5–2.2	1.4–2.1		
Mean ±SD	1.910± 0.288	1.710± 0.251		

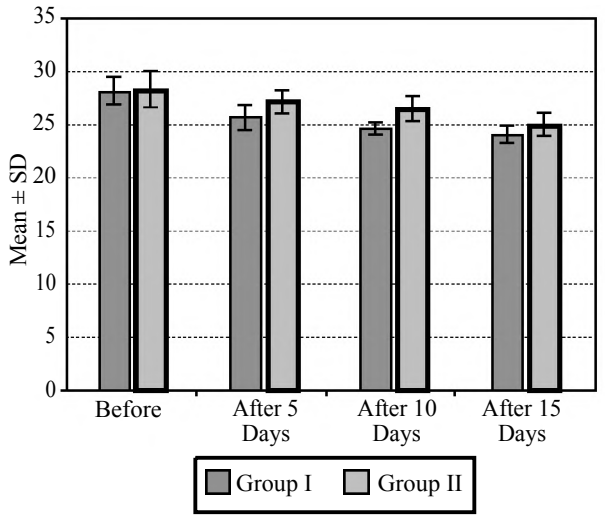

Fig. (1): Comparison between studied groups as regard abdominal girth.

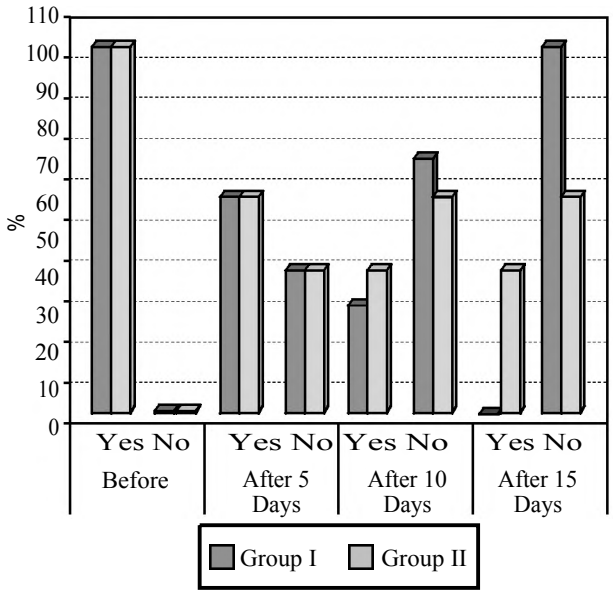

Fig. (2): Comparison between studied groups as regard feeding residual.

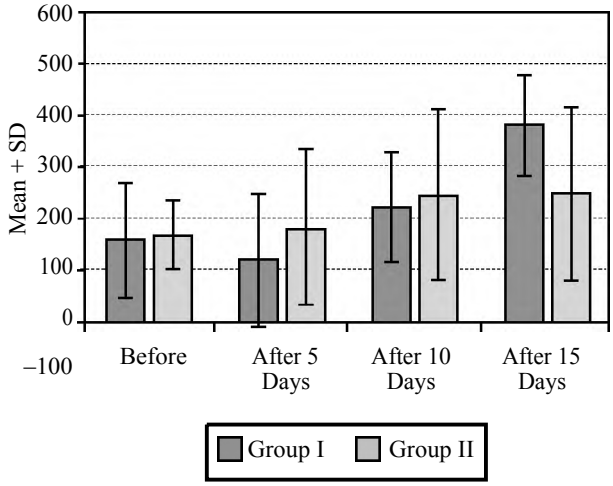

Fig. (3): Comparison between studied groups as regard platelets count.

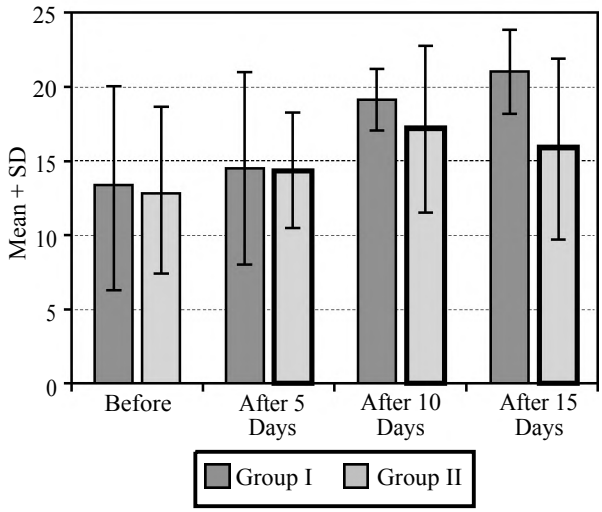

Fig. (4): Comparison between studied groups as regard serum bicarbonate level.

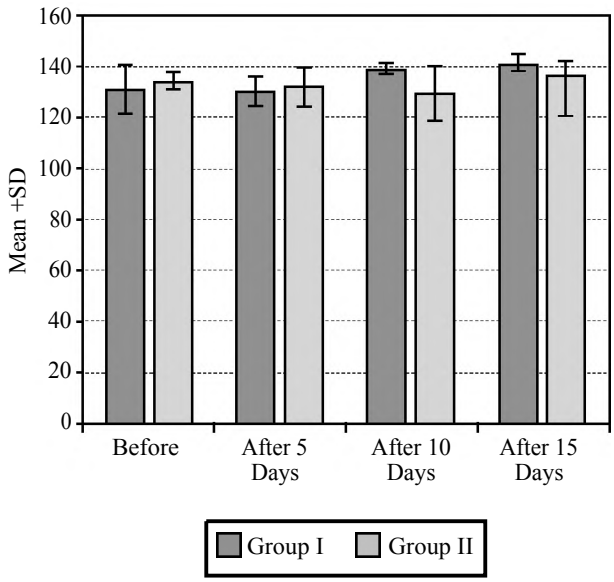

Fig. (5): Comparison between studied groups regard serum sodium.

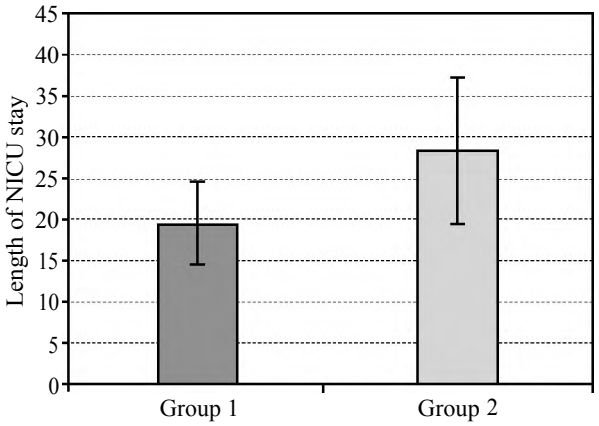

Fig. (6): Comparison between both groupsas regard length of NICU stay.

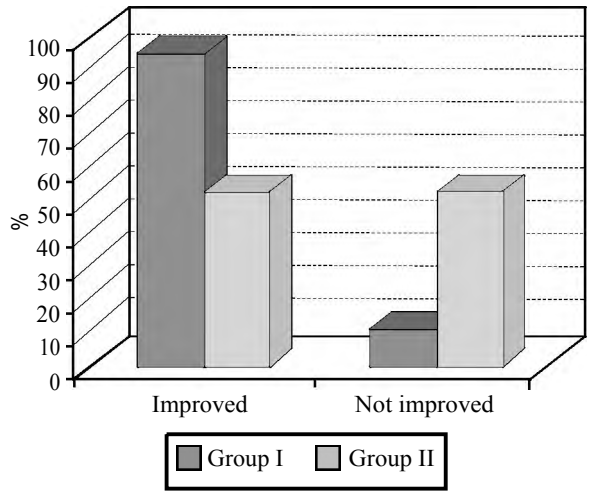

Fig. (7): Comparison between studied groups as regardoutcome of NEC.

Discussion

In our study there was statistically no significant difference among all studied groups as regard demographic data (gestational age, weight and gender) and this in agreement with El-Farargy et al., who used melatonin as an adjuvant therapy in neonatal sepsis [11].

In our study there was statistically significant difference between both groups as regard vomiting and feeding residual as there was more improvement in group I treated with melatonin more than group II and this is inagreement with Pereira who reported that dietary supplementation of melatonin resulted in remarkable remission in gastroesophageal reflux disease [12]. Kesik et al., showed the healing effectof melatonin in ischemia-reperfusion model in rats so decreased symptoms and signs of GIT disturbances [13].

As regard abdominal girth we found that there was Significant difference between both groups on comparison between before and after receiving treatment as there was significant improvement and decreased abdominal girth to normal range in group I more than group II This agreed with Esteban-Zubero et al., [14] who studied role of melatonin as aco-adjuvant treatment in colonic diseases.

There was significant difference as regard platelets count between both groups as there was significant improvement in thrombocytopenia in group I who received melatonin more than group II and in agreement withLissoni et al., [15]. Who showed protective effects on platelet recovery by administration of melatonin have already been shown in an irradiated mouse model and in patients with thrombocytopenia. Also in agreement with this study El-Farargy and Soliman [16]. Who used melatonin asadjuvant therapy in necrotizing enterocolitis in neonates.

The present study found significant difference in metaboli cacidosis, hyponatremia between preterm neonates at the onset of the research and after 5, 10 and 15 days ofonset as there was significant improvement in group I who received melatonin more than group II in agreement with this stud El-Farargy and Soliman [16] who used melatonin asadjuvant therapy in necrotizing enterocolitis in neonates.

As regard outcome of NEC it was observed that In Group I there were 90% cases improved and 10% case not improved but in Group II there were 50% of cases improved and 50% of cases not improved and this showed significantly improvement of cases in group I who received melatonin than group II who received antibiotics only. As the NEC is apart of sepsis so this is in agreement with Gitto et al., [8] who had shown that melatonin has anti-inflamatory effect in neonates suffering from neonatal sepsis if it is added as an adjuvant therapy and there was significant improvement in group suffering from neonatal sepsis treated with melatonin and antibiotics.

There was significant difference between melatonin and traditional therapy groups as regard length of stay in hospital as group I who received melatonin stay for ashorter period in NICU compared to group II who received traditional therapy without melatonin.

Conclusion:

Administration of melatonin as an adjuvant therapy in the treatment of NEC in preterm neonates is associated with improvement of clinical and laboratory outcome.

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Conflicts of interest:

No conflicts of interest declared.

Authors' contributions:

All authors had equal role in design, work, statistical analysis and manuscript writing. All authors have approved the final article work.

References

1- SRINIVASAN P.S., BRANDLER M.D., D'SOUZA R.D., et al. : Necrotizing enterocolitis. Clin. Perinatol., 35: 251-272, 2008.

2- MARSEGLIA L., D'ANGELO G., MANTI S., et al.: Oxidative stress-mediated aging during the fetal and perinatal periods. Oxid. Med. Cell. Longev., 358-375, 2014.

3- NEU J., YOUNG C., SHARMA R., et al.: Necrotizing enterocolitis: The search for a unifying pathogenic theory leading to prevention. Pediatr. Clin. North. Am., 43: 409-432, 1996.

4- HUNTER C.J., UPPERMAN J.S., FORD H.R., et al.: Understanding the susceptibility of the premature infant to necrotizing enterocolitis (NEC). Pediatr. Res., 63: 117-123, 2008.

5- REITER R.J., PAREDES S.D., MANCHESTER L.C., et al.: Reducing oxidativelnitrosative stress: A newly-discovered genre for melatonin. Crit. Rev. Biochem. Mol. Biol., 44: 175-200, 2009.

6- BRZEZINSKI A., CLAUSTRAT B., LESTON J., et al.: Melatonin in humans. New England Journal of Medicine, 336 (3): 186-195, 1997.

7- HARDELAND R., CARDINALI D.P., SRINIVASAN V., et al.: Melatonin-a pleiotropic, orchestrating regulator molecule. Prog. Neurobiol., 93: 350-84, 2011.

8- GITTO E., MARSEGLIA L., MANTI S., et al.: Protective ole of Melatonin in Neonatal Diseases. Oxid. Med. Cell. Longev., 980374: 1-9, 2013.

9- PARADIES G., PETROSILLO G., PARADIES V., et al.: Melatonin, cardiolipin and mitochondrial bioenergetics in health and disease. J. Pineal. Res., 48: 297-310, 2010.

10- GUVEN A., UYSAL B., GUNDOGDU G., et al.: Melatonin ameliorates necrotizingenterocolitis in a neonatalrat model. Pediatr. J. Surg., 46: 2101-2107, 2011.

11- ELFARAGY M., EL-SHARKAWY H.M. and ATTIA G.F.: Use f melatonin as an adjuvant therapy in neonatal sepsis. J Neonatal Perinatal Med., 8: 227-32, 2015.

12- PEREIRA R.D.S.: Regression of gasroesophageal reflux disease symptoms using dietary supplementation with melatonin, vitamins and amino acids: Comparison with omeprazole. J. Pineal. Res., 41: 195-200, 2006.

13- KESIK V., GUVEN A., VURUCU S., et al.: Melatonin and 1400 W ameliorate both intestinal and remote organ injury following mesenteric ischemia/reperfusion. J. Surg. Res., 157: 97-105, 2009.

14- ESTEBAN-ZUBERO E., LOPEZ-PINGARRON L., ALATORRE-JIMENEZ M.A., et al.: Melatonin role as a co-adjuvant treatment in colonic diseases. National Institutes of Health. Life Sciences, 170: 72-81, 2017.

15- LISSONI P., TANCINI G., BARNI S., et al.: The pineal hormone melatonin in hematology and its potential efficacy in the treatment of thrombocytopenia, Recenti. Prog. Med. 87: 582-585, 1996.

16- ALY H., ELMAHDY H., EL-DIB M., et al.: Melatonin use for neuroprotection in perinatal asphyxia: A randomized controlled pilot study. Journal of Perinatology, 35: 186-191, 2015.

دور الميلاتونين فى علاج ناخر الأمعاء فى الأطفال حديثى الولادة غير مكتملى النمو

يعد مرض ناخر الأمعاء ما يطرئ على جراحة الجهاز الهضمى فى الأطفل الخدع أقل من ٣٧ أسبوعا وأقل من ١٥٠٠جم. ناخر الأمعاء هو مرض إلتهابى يصيب القناة الهضمية ناتج عن مسببات عديدة تشمل الأكسدة والأستجابة الإلتهابية المبالغ فيها عن الأستعمار البكتيرى الغير طبيعى. يعتبر الميلاتونين هو أعلى مضادات الأكسدة الفعالة وبالتالى قد يكون مفيد فى علاج حديثى الولادةالمصابين بناخر الأمعاء.

الهدف من الدراسة: الهدف من هذه الدراسة هو تقييم دور الميلاتونين فى علاج ناخر الأمعاء.

المرضى وطرق البحث: تم عمل هذه الدراسة على ٢٠ من الأطفال حديثى الولادة غير مكتملى النمو تم تقسيمهم إلى مجموعتين: المجموعة الأولى تشمل ١٠حديثى الولادة يعانون من ناخر الأمعاء ويتم علاجهم بالمضادات الحيوية والميلاتونين والمجموعة الثانية تشمل ١٠حديثى الولادة يعانون من ناخر الأمعاء ويتم علاجهم بالمضادات الحيوية فقط فى حضانات مستشفى طنطا الجامعى العالمى.

النتائج: لوحظ أن المجموعة التى تم إضافة الميلاتونين إلى العلاج تحسنت بشكل ملحوظ وأنخفضت أعراض المرض (القئ، إنتفاخ البطن، عدم إستقرار الحرارة) عن المجموعة الثانية. المجموعة الأولى التى تم علاجها بالميلاتونين لوحظ بها تحسن فى الأشعة وأصبحت طبيعية فى فترة قصيرة عن المجموعة الثانية. إرتفاع نسبة الصفائح الدموية ونسبة الصوديوم فى الدم ووصولها المعدلات الطبيعية فى المجموعة الأولى عنها فى المجموعة الثانية. لوحظ زيادة ذو دلالة إحصائية فى نسبة الشفاء فى المجموعة الأولى عنها فى المجموعة الثانية. لوحظ أن فترة العلاج والإقامة بالمستشفى إمتدت لفترة أطول فى المجموعة الثانية عنها فى المجموعة الأولى.

الأستنتاج: يعتبر الميلاتونين له دور فى علاج ناخر الأمعاء فى الأطفال حديثى الولادة غير مكتملى النمو.

التوصيات: نحن نوصى إضافة الميلاتونين فى علاج ناخر الأمعاء فى الأطفال حديثى الولادة غير مكتملى النمو.