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Melatonin Supplementation as Adjuvant Therapy for the Prevention of Bronchopulmonary Dysplasia in Neonates

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ABSTRACT

Background: Neonatal bronchopulmonary dysplasia (BPD) is a chronic chest disease caused by prolonged ventilation and oxygenation which leads to neonatal disability.

Methods: It was a prospective randomized clinical trial (RCT) (Study ID: TCTR20191211004) which was conducted in Tanta University Hospital (TUH) from July 2016 to March 2018 on 100 preterm neonates who exhibited severe respiratory distress (RD) on mechanical ventilation (MV). The studied neonates were assigned to two groups: group one which received melatonin supplementation and group two which did not. Urinary β2-microglobulin (B2M) and serum Krebs von den Lungen-6 (KL-6) levels were measured 3 and 10 days after hospitalization. The length of neonates' stay in incubator was determined, and the number of newborns with established BPD was calculated.

Results: Significant decreases were detected in urinary B2M and serum KL-6 levels of neonates in group one who received melatonin, as compared to their counterparts in group two who did not take melatonin ($P< 0.05$). In addition, there was a significant decline in the length of incubator stay of neonates in group one, in comparison to that of newborns in group two ($P<0.05$). Moreover, neonates in group one who received melatonin displayed a significant decline in the development of established cases of BPD, as compared to group two who did not take melatonin ($P<0.05$).

Conclusion: As evidenced by the obtained results, melatonin supplementation could be used as adjuvant therapy for the prevention of BPD in preterm neonates. Nonetheless, further studies involving a larger number of neonates must be performed on this topic in order to recommend melatonin administration for ventilated premature neonates who are susceptible to the development of neonatal BPD.

Keywords: Bronchopulmonary dysplasia, Melatonin, Neonate

Introduction

Bronchopulmonary dysplasia (BPD) is a a form of chronic lung disease which mostly occurs in premature newborns who are exposed to mechanical ventilation (MV) and prolonged Oxygen therapy . BPD is a chronic chest disease that occurs mainly in preterm neonates when the normal structure of the lung is replaced by fibrous tissue, the function of the lung is impaired, and gas exchange is affected causing neonatal respiratory distress (RD). BPD is considered the most frequent chronic complication that occurs in premature neonates and the most common chronic chest disease which has been reported in these neonates (1, 2).

BPD is diagnosed as a condition with a chronic O2 requirement due to prolonged O2 exposure for more than 28 days with chest X-rays revealing constant opacification or increased density (3). BPD is classified as mild, moderate, and severe, according to the level of O2 concentration needed to maintain normal respiration without RD (4).

Mild BPD is a neonatal management with >21% O2 for at least 4 weeks (28 days) plus the ability to respire room air without RD within 36 weeks gestational age (GA) or discharge (in <32 weeks) or plus the ability to respire room air

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without RD at the age of >28 d or at discharge (in ≥32 weeks) (3). Moderate BPD is a neonatal management with >21% O2 for at least 4 weeks (28 days) plus the ability to respire <30% O2 without RD in 36 weeks GA or discharge (in <32 weeks) or O2 requirement(<30%) at the age of >28 d or at discharge (in ≥32 weeks) (3). Finally, severe BPD is a neonatal management with >21% O2 for at least 4 weeks (28 days) plus the need for ≥30% O2 for normal respiration without RD in 36 GA or discharge (in <32 weeks) or O2 requirement (≥30%)at age of >28 d or at discharge (in ≥32 weeks) (4).

Krebs von den Lungen-6 (KL-6) is a glycoprotein that is formed by type II pneumocytes. Its presence indicates the occurrence and severity of several lung diseases and is considered an excellent predictor marker for the occurrence of neonatal BPD (5). B2M is a protein that is present on the cell surface of almost all cells in the body and is secreted by B lymphocytes into the serum. β2-microglobulin (B2M) consists of two beta-sheet immunoglobulins which are found in many body fluids, especially urine. The urinary B2M level is a non-invasive, easy marker of chronic chest disease and is considered an excellent predictor marker for the occurrence of neonatal BPD (6).

Melatonin is considered an endogenous indolamine that is mainly synthesized in the pineal gland from serotonin which serves as a neurotransmitter (7, 8). Melatonin is a very potent antioxidant which acts as a free-radical scavenger (9). Free radicals are derived from elevated oxygen and oxygen metabolites which may damage cells in individuals exposed to elevated oxygen (10). Melatonin which is an effective and powerful antioxidant acts as a detoxification agent to counteract oxidative stress (11).

The present study aimed to demonstrate the role of melatonin as adjuvant therapy in the prevention and management of subsequent BPD in preterm neonates.

Methods

The current research was a prospective randomized clinical trial (RCT) which was performed in Tanta University Hospital (TUH) from July 2016 to March 2018 on 100 neonates with severe RD who needed MV and were exposed to FIO2>21%. The research was approved by the Ethical Committee of the College of Medicine, TUH, and the informed consent was taken from the fathers of all neonates present in this study. A total number of 100 neonates were divided into two groups, and every neonate was assigned a number. Subsequently, odd-numbered cases were allocated to group one and even-numbered ones to group two. Group one consisted of 50 preterm neonates who received melatonin supplementation, while group two included 50 preterm newborns who did not receive melatonin.

The elevation of KL-6 is indicative of the occurrence and severity of several lung diseases and can be regarded as an excellent predictor marker for the occurrence of neonatal BPD (5). On the other hand, the elevation of urinary B2M levels in established cases of neonatal BPD has been proven. Therefore, urinary B2M is considered an excellent marker in the prediction of neonatal BPD development in premature neonates. (12-14).

Plasma KL-6 and urinary B2-microglobulin were measured on the 3rd and 10th days of hospital admissions and used as an excellent predictor marker for the development of neonatal BPD in both groups. Established cases of BPD were diagnosed as a condition with a chronic O2 requirement due to prolonged O2 exposure with chest x-rays revealing constant opacification or increased density (3).

The neonates in group one (n=50) received melatonin at a dose of 10 mg/kg once daily for 5 days. Melatonin tablets (3 mg per tablet; Puritan's Pride®, Oakdale, NY, USA) were crushed, dissolved in 5 ml distilled water, and administered through an orogastric tube (15,16).

Inclusion and exclusion criteria

Inclusion criteria entailed preterm neonates with severe RD who needed MV and were exposed to FIO2>21%. On the other hand, exclusion criteria included: 1) full-term neonates, 2) neonatal sepsis, 3) congenital anomalies, 4) death (three cases in group one and six neonates in group two and they were replaced by other neonates according to inclusion criteria to maintain 50 neonates in each group), 5) transfer to another hospital (two cases in group one and three newborns in group two, and they were replaced by other neonates according to inclusion criteria to maintain 50 neonates in each group).

Determination of plasma KL-6

Blood samples were obtained from any superficial vein using an aseptic technique by needle puncture on an EDTA tube. Subsequently, they were immediately centrifuged at 3000×g for 10 min at 4°C to obtain plasma and then stored at -80°C until the assessment. . The plasma level of

KL-6 was measured by an enzyme-linked immunosorbent assay (ELISA) using a KL-6 antibody kit (Kamiya Biomedical Co.®, USA) according to the manufacturer's instructions using an Awareness Technology® (USA) ELISA Reader. The KL-6 concentration was expressed in U/ml.

Estimation of urinary Beta-2-microglobulin

The examined neonatal urine samples were collected using urine collection bags. The urine samples were centrifuged immediately at 3000×g for 10 min at 4°C to obtain the supernatant which was stored at -80°C until the assessment. All abnormal samples which showed protein, blood, bacteria, or abnormal sediments were excluded. The urinary B2M level was estimated by ELISA using commercial kits (ORGENTEC Diagnostika®, Germany), in accordance with the manufacturer's instructions using Awareness Technology® (USA) ELISA Reader. The B2M concentration was expressed in mg/L.

Results

Statistical analysis

The obtained data were analyzed in SPSS software (version 21) using the mean, standard deviation, and chi-square test. The independent-samples t-test was used for the comparison between the two groups. Paired Samples t-test was applied for the comparison within the same group at different times. In addition, Chi-square (X2) test was used for the comparison between the two groups regarding the qualitative data. A p-value less than 0.05 was considered statistically significant.

The studied neonates included 100 cases who were assigned to group one which consisted of 50 preterm neonates who received melatonin supplementation and group two which included 50 preterm neonates who did not receive melatonin.

Table 1 demonstrates group one which included 50 preterm neonates (32.6±1.1 weeks) who weighed 1768.8±92 g, were admitted with severe RD with a Down score of 8.25±0.15, were incubated on MV for a duration of 9.9±0.1 days, were exposed to FIO2 >21% for 8.15±0.15 days, and a daily administration of melatonin was performed at a dosage of 10 mg/kg for 5 days during the 4th to 9th days of hospitalization. Table 1 also displays group two which included 50 preterm neonates (32.7±1.15 weeks), who weighed 1772.9±89 grams, were admitted with severe RD and a Down score of 8.2±0.1, were incubated on MV for a duration of 9.85±0.15 days, were exposed to FIO2>21% for 8.2±0.1 days, and did not receive melatonin. There were no significant contrasts in weight, gestational age, Down score, duration of MV, duration of exposure to FIO2>21%, mode of delivery, and gender between group one and group two, and the p-value was obtained as >0.05.

Table 2 indicates that in group one, serum KL-6 on the 3rd day of hospitalization was calculated at 102.7±43.6 U/ml, while serum KL-6 on the 10th day of hospital admission was measured at 78.6±31.9 U/ml with a significant decline on the 10th day, as compared to the 3rd day of hospital stay (P<0.05), whereas in group two, serum KL-6 on the 3rd day of hospitalization was obtained as

Table 1. Comparative characteristics between studied groups

		Group 1 (n=50)		Group 2 (n=50)		Test	P-value
Weight (g)	Mean±SD	1768.8±92		1772.9 ± 89		T: 0.228	0.821
Gestational age (weeks)	Mean±SD	32.6±1.1		32.7±1.15		T: 0.441	0.658
Down score	Mean±SD	8.25±0.15		8.21±0.11		T: 1.518	0.132
Duration of mechanical ventilation (days)	Mean±SD	9.9±0.1		9.85±0.15		T: 1.955	0.053
Duration of exposure to FI02 > 21% (days)	Mean±SD	8.15±0.15		8.12±0.13		T: 1.062	0.288
	N	%	N	%	X^2	P value	N
Mode of delivery	NVD	12	24	13	26	0.049	0.817
	CS	38	76	37	74		
Gender	Male	32	64	34	68	0.182	0.673
	Female	18	36	16	32		

*P is significant if <0.05. NVD: Normal vaginal delivery, CS: Caesarean section

Table 2. Plasma KL-6 and urinary B2-microglobulin on the 3rd and 10th days of admission

		Group one (n=50)	Group two (n=50)	t-test	P-value
Serum KL-6 on the 3rd day (U/ml)	Mean±SD	102.7±43.6	101.6 ±42.7	0.134	0.899
Serum KL-6 on the 10th day (U/ml)	Mean±SD	78.6±31.9	104.7±42.9	3.453	0.001*
P-value		0.003*	0.718		
Urinary B2-microglobulin on the 3rd day (mg/L)	Mean±SD	3.4±1.9	3.2±1.7	0.549	0.580
Urinary B2-microglobulin on the 10th day (mg/L)	Mean±SD	1.9±1.2	3.5±1.8	4.443	0.001*
P-value		0.001*	0.407		

*P is significant if < 0.05.

Table 3. Duration of incubator stay of neonates

		Group one (n=50)	Group two (n=50)	t-test	P-value
Duration of incubator stay of neonates (days)	Mean±SD	23±9	31±10	4.203	0.001*

*P is significant if < 0.05.

Table 4. Number of cases that developed bronchopulmonary dysplasia in both groups

	Group 1 (n=50)	Group 2 (n=50)	t test	P value
Number of cases of established bronchopulmonary dysplasia	2 (4%)	8 (16%)	4.001	0.046*

*P is significant if < 0.05.

01.6±42.7 U/ml, and the serum KL-6 level on the 10th day of hospital stay was measured at 104.7±42.9 U/ml with no significant contrasts (P>0.05). Moreover, there were no significant contrasts in serum KL-6 between the groups (P>0.05) on the 3rd day of hospital stay. Nevertheless, a significant difference was detected in serum KL-6 between the groups (P<0.05) on the 10th day of hospitalization.

Table 2 illustrates that in group one, urinary B2M on the 3rd day of admission was calculated at 3.4±1.9 mg/L, while urinary B2M on the 10th day of hospital stay was measured at 1.9±1.2 mg/L with a significant decrease on the 10th day, as compared to the 3rd day of hospitalization (P<0.05). In group two, urinary B2M on the 3rd day of hospital stay was obtained as 3.2±1.7 mg/L, and urinary B2M on the 10th day of hospitalization was measured at 3.5±1.8 mg/L with no significant contrast (P>0.05). In addition, there were no significant contrasts in urinary B2M between the groups (P>0.05) on the 3rd day of hospital stay. Nonetheless, a significant difference was observed in the urinary B2M between the two groups (P<0.05) on the 10th day of hospital stay.

Table 3 demonstrates that the duration of incubator stay of neonates in group one was 23±9 days, while it was reported as 31±10 days in the neonates in group two indicating a statistically significant difference between the two groups (P<0.05).

Table 4 displays that there were two cases of BPD in group one accounting for 4% of the total number of neonates in group one. In addition, eight cases of BPD were reported in group two representing 16% of the total number of neonates in group two with a statistically significant difference between the two groups (P<0.05).

Discussion

BPD is a chronic respiratory disease that most often occurs in low-weight or premature neonates due to prolonged exposure to elevated oxygen concentration or ventilatory support. This long exposure results in the release of oxygen-free radicals and other harmful oxidants which counteract the hypoxemia resulting from RD occuring in premature neonates due to many diseases, especially respiratory distress syndrome (RDS). (1)

In a prospective study, cord blood and plasma KL-6 were identified as potential biomarkers for BPD, and KL-6 has been approved by Japan's health insurance program as a diagnostic marker for interstitial lung disease. Unlike non-specific markers of inflammation or fibrosis, KL-6 is a specific marker of inflammation and fibrosis and reflects the severity of pulmonary affection; therefore, it is a reliable marker for the occurrence of BPD (5).

The elevation of urinary B2M levels in established cases of neonatal BPD has been proven, and so urinary B2M is considered as an excellent marker in predicting the development of neonatal BPD in premature neonates. (12-14).Prolonged exposure of preterm neonates to elevated levels of oxygen will cause oxidative stress with the production of oxygen-free radicals, these harmful oxygen-free radicals and other harmful oxidants, in addition to the condition of oxidative stress will causes a chronic inflammation in the lung leading to the development of neonatal BPD, this harmful effect of prolonged O2 could be counteracted by strong and safe antioxidants like melatonin. (15,16).

Melatonin is selected as a potent antioxidant which protects lung tissue against the adverse effect of O2 free radicals released from prolonged exposure to high levels of O2 leading to the development of neonatal BPD (17). Melatonin can be of great help in counteracting chronic inflammation of lung tissue which occurs in neonatal BPD as a result of prolonged exposure of lung tissues of the premature neonates to high levels of oxygen (18, 19).

In line with the results of the present study, other investigations revealed that neonates with BPD who are treated with melatonin had lower levels of pro-inflammatory cytokines which are markers of chronic inflammation which occurs in lung tissues (20). Some studies concluded that melatonin administration was associated with a

decline in the inflammatory cytokines and a substantial improvement in the clinical outcome of BPD. These studies had attributed these beneficial results to the anti-inflammatory effect of melatonin (21, 22).

Consistent with the present study, an investigation conducted on rats concluded that melatonin could serve as an excellent antioxidant which counteracts the harmful oxidants released from sustained exposure of lung tissues to high levels of oxygen. Therefore, it protects lung tissues from the damage inflicted by these harmful oxidants (23). B2M serum levels reflect the condition of lymphocytic activation that occurs in inflammation. Consequently, elevated serum or urinary B2M levels could be used as a good marker of chronic inflammation, such as chronic chest disease or BPD. Therefore, in the current study, B2M was used as an excellent predictor for the development of neonatal BPD (24).

Numerous studies have proven that elevated urinary B2M and serum KL-6 could be used as an excellent predictor for the early neonatal BPD diagnosis (25, 26). Serum levels of KL-6 are correlated with the occurrence and severity of neonatal BPD (27, 28). In another study, the cord blood and plasma levels of KL-6 proved to be a good marker for BPD (29). The present study revealed that the levels of urinary B2M decreased after melatonin administration in the neonates of group one who received melatonin. Therefore, it can be concluded that melatonin administration leads to a decline in urinary B2M which is a good marker for the occurrence of neonatal BPD. On the contrary, there was an elevation of urinary B2M in neonates of group two on the 10th day, as compared to the 3rd day of hospitalization.

In addition, the current study revealed that the level of serum KL-6 in the neonates of group one who received melatonin was 102.7±43.6 U/ml on the 3rd day of hospital stay. Moreover, there was a decline in the level of serum KL-6 after melatonin administration to 78.6±31.9 U/ml on the 10th day of hospital stay indicating that melatonin leads to a decline in serum KL-6 which is a good marker for the occurrence of neonatal BPD. Conversely, there was an elevation of serum KL-6 in the neonates of group two on the 10th day, as compared to the 3rd day of hospital stay.

Limitations

Every study has some limitations which should be addressed in the paper. The major limitation of the present study is the limited number of neonates; therefore, other studies should be conducted using a larger number of neonates.

Conclusion

As evidenced by the obtained results, melatonin supplementation could be used as adjuvant therapy for the prevention of BPD in preterm neonates. Nevertheless, further studies involving a larger number of neonates must be performed on this topic in order to recommend melatonin administration for ventilated premature neonates who are susceptible to the development of neonatal BPD.

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Conflicts of interest

The authors declare that they have no conflict of interest regarding the publication of this article.

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