EXPERIMENTAL STUDY

The effects of melatonin on the healing of burn wounds in pinealectomized rats

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ABSTRACT

BACKGROUND: The present study aims to investigate the favorable effects of melatonin on burn wound healing in rats.

METHODS: In this study, forty Wistar-albino-type male rats were divided into four groups. Group 1 was the control group, Group 2 rats were treated using exogenous melatonin, Group 3 rats were pinealectomized, and Group 4 rats were pinealectomized then treated with exogenous melatonin. In all groups, a deep second-degree burn was created on the backs of the rats with a metal plate heated in boiling water. We monitored the progress of burn healing for seven days. At the end of them, we evaluated hydroxyproline levels, type III collagen, edema, inflammatory infiltration, congestion, vascular proliferation, fibrosis, the thickness of the zone of stasis and the epithelium to assess the progress of healing.

RESULTS: The zone of stasis was less thick in Group 2 than the other groups (p=0.009). Type III collagen dyeing (p=0.031), fibrosis (p=0.011) and edema (p=0.031) were higher in Group 2 than the other groups. Congestion was higher in the control group than Group 4 (p=0.031). Other evaluated parameters showed no significant differences among the groups.

CONCLUSION: In this study, it was noted that once total melatonin levels exceeded a certain threshold, a preventive effect was exerted on burn wound damage progression by reducing the zone of stasis. Melatonin may also prevent the development of hypertrophic scarring. Melatonin may be a potential therapeutic option that can supplement traditional treatment in burn wounds; however, further studies with higher doses of exogenous melatonin administered over longer periods are needed to further evaluate the effects noted in this study.

Keywords: Burn; endogenous melatonin; exogenous melatonin; pinealectomy; wound.

INTRODUCTION

In burn wound healing, the progression of the tissue injury determines the mortality, morbidity and treatment outcomes. Jackson described burn wounds as having three distinct zones based on the severity of destruction and blood flow alterations.[1] The zone of coagulation is the central zone characterized by necrosis. The zone of coagulation is encircled by the zone of stasis, which is indirectly affected by the trauma, and the zone of stasis is surrounded by a zone of hyperemia characterized by increased blood flow. Salvaging the zone of stasis can prevent an increase in the depth and the width of the burn injury area, thereby significantly reduce the risks of mortality and morbidity.[2–4] The underlying cause of progressive tissue injury in this zone is the systematic activation of neutrophils due to the production of free oxygen radicals[2] and studies report that antioxidants can prevent this progressive effect.[3]

Melatonin, an antioxidant hormone produced in the pineal gland, increases the activity of enzymes like glutathione peroxidase, superoxide dismutase, and nitric oxide synthase. Melatonin also directly affects free oxygen radicals[5] by scavenging free radicals more effectively than other antioxidants.[6]

Given the role of free oxygen radicals in burn wound progression, exogenous melatonin may be an alternative to traditional burn injury treatments. To our knowledge, there are

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no published studies that examine the effects of endogenous melatonin and exogenous melatonin on burn healing. Therefore, in this study, we investigated the effects of the basal release of melatonin, i.e., endogenous melatonin levels, in our pinealectomy group, and whether explored exogenous melatonin has favorable effects on burn wound healing in the groups administered exogenous melatonin.

MATERIALS AND METHODS

With the prediction of the difference in the medium effect size accepted for animal experiments in groups as statistically significant, we determined our sample size as 24 rats for 95% power at 0.05 alpha significance level. However, due to the increased mortality and morbidity risk of the pinealectomy procedure, we increased the sample size to 40 animals. Therefore, 40 Wistar-albino-type male rats with body weights ranging from 350 g to 500 g were used in this study.

Five rats per cage were housed in a temperature-controlled room at 22°C ± 1°C and 50% ± 5% humidity on a 12-hour dark-light cycle with free access to water and food. Rats were randomized into four groups (10 rats per group), and burn wounds were created on the backs of all rats in all groups. Group 1 was the control group that received no treatment. Group 2 rats received exogenous melatonin (ExM). Group 3 rats received pinealectomy (Px) and no treatment, and Group 4 rats received Px+ExM. This study was approved by the local ethics committee of the university (project no: 2012/121518019).

Burn Wound Creation

Before conducting this study, we reviewed the literature and verified our chosen method with a pilot study in which we tested our method for burn wound creation on one rat. This study was started only after we confirmed the burn model and the degree of the burn using histopathological examination in this pilot application. In all rats, burns were created under general anesthesia induced with intraperitoneal ketamine hydrochloride (8 mg/100 g) and xylazine hydrochloride (1 mg/100 g). The right side of the back skin was shaved in all rats. A circular metal plate with a 1.5-cm-diameter was immersed in boiling water for five minutes measured at 100°C and then placed on the shaved backs of each rat for 15 seconds (without applying pressure) to produce deep second-degree burns. The reason for using a circular metal plate was to assess the wound contraction easily during healing. Burn wounds were left open for the duration of this study, and no topical or other preparations were applied.

Pinealectomy

Pinealectomy was performed on rats in Groups 3 and 4 immediately before burn-wound creation. Anesthetized rats were positioned on their abdomens and stabilized. Their heads were cleaned gently with polyvinylpyrrolidone iodine, and a 2-cm incision was made along the midline of the hairless scalp, right behind the eyes. We exposed the junction of the transverse and sagittal sutures and formed an 8-mm diameter circular bone flap using a reverse conic dental drill (Fig. 1a). We cut the dura bilaterally up to the sagittal sinus. The anterior third of the sagittal sinus was doubly ligated with 8/0 polypropylene sutures (Fig. 1b). By folding the caudal portion of the ligated sagittal sinus posteriorly, the pineal gland was exposed beneath the junction of the transverse and sagittal sinuses (Fig. 1c). The gland was carefully removed, the bone flap was replaced, and the skin was stitched closed. All excised pineal glands were confirmed by histopathological evaluation.

Melatonin Administration

Powdered melatonin (16.5 mg; Merck Schuchardt OHG, Hohenbrunn, Germany) was dissolved in 0.5 cm^3 100% ethanol; then diluted with 5 cm^3 physiological saline to reduce the ethanol concentration to 10%. Melatonin was prepared freshly for each case in a dark environment and injected intraperitoneally to the rats in Groups 2 and 4 at a dose of 10 mg/kg/day between 16:00 and 17:00 hours for seven days.

Removal of Burn Wound Tissue

On a postoperative day seven, burn wounds were excised using full-thickness excision under general anesthesia to collect the specimen. Each specimen was dissected into two equal pieces: one piece was fixed in 10% buffered formalin for histopathological analysis, and the other was washed with cold 0.9% NaCl and placed in Eppendorf tubes maintained at -80°C for biochemical analysis. All rats were sacrificed after this procedure.

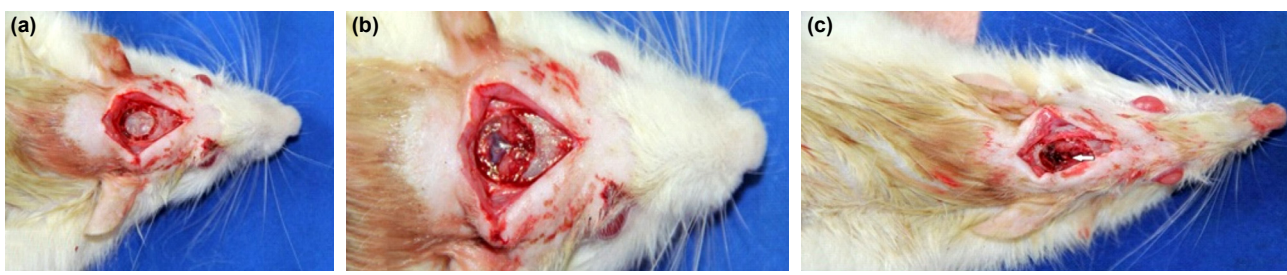

Figure 1. (a) Circular craniotomy via reverse conic dental drill. **(b)** Ligation of the anterior third of superior sagittal sinus. **(c)** The pineal gland made visible by reflecting the caudal portion of the ligated sagittal suture posteriorly (white arrow).

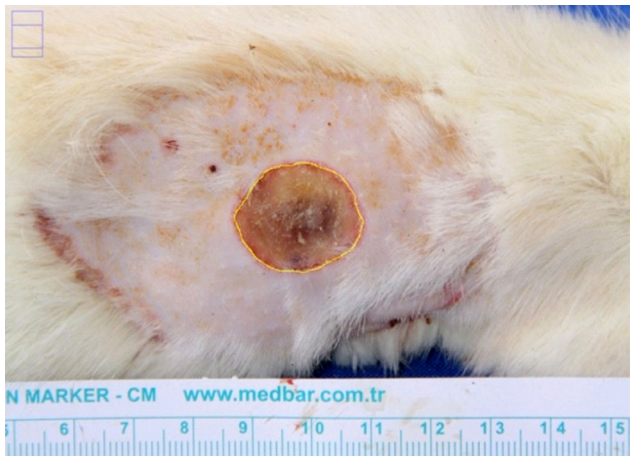

Figure 2. Analysis of burn wound surface area using ImageJ software.

Evaluation

Photo Analysis

Burn wounds were digitally photographed (Canon EOS60D SLR, 18 megapixels, Canon USA, Japan) on a daily basis, next to a millimetric ruler in all groups under diethyl ether anesthesia. Surface areas of burn wounds were analyzed using ImageJ software (NIH, Bethesda, Maryland, USA). We calibrated the wound area using the millimetric ruler, and the surface area was calculated in square millimeters (Fig. 2). The burn wound margins for rats in each group were traced with a fine-resolution computer mouse on day one and day seven, and the burn wound surface area was calculated. Healing was evaluated based on the progress observed in the burn wound surface area between days one and seven. We also compared the mean progress of healing achieved during this period in each group. Progress of healing was calculated based on the difference between the day one and day seven measurements of the burn wound area in each rat, and the mean healed areas of the groups were compared.

Biochemical Analysis

Specimens were weighed and homogenized in 2N NaOH/g wet tissue. Hydroxyproline levels of the specimens were blind-measured according to the method described by Reddy and Enwermeka.[7] Results were recorded as µg/g wet tissue.

Histopathological and Immunohistochemical Analysis

Specimens were fixed in 10% buffered formalin and embedded in paraffin media. Micron sections (5 µm) were deparaffinized and processed to rehydration, followed by staining with Hematoxylin-Eosin dye (Surgipath, 01562E, 01602E, Peterborough, UK) for histopathological analysis.

For immunochemical staining, specimens were prepared using the avidin-biotin peroxidase method (HRP, Thermo Scientific, UK). Collagen anti-type III rat monoclonal protein receptor antibody Thermo Scientific, Clone 1E7-D7 was raised for immunohistochemical analysis. Brown-colored staining of more than 10% was considered positive. Sections stained with histopathological and immunohistochemical methods were examined using light microscopy (Olympus BX40 light microscope). Thicknesses of the zone of stasis and the epithelium were measured from five different points using the Image Analyzing System (BAB Bs 200proP; Fig. 3a, b). We determined the average in microns.

Vascular proliferation, edema, congestion, fibrosis and inflammatory infiltration were evaluated. Each parameter was scored as negative if none present, + (minimal) if present only on one site, ++ (mild) if present on two sites and +++ (significant) if present on three or more sites, to assess the extent of modification.

The degree of immunohistochemical staining was semi-quantitatively evaluated. Type III collagen staining was scored neg-

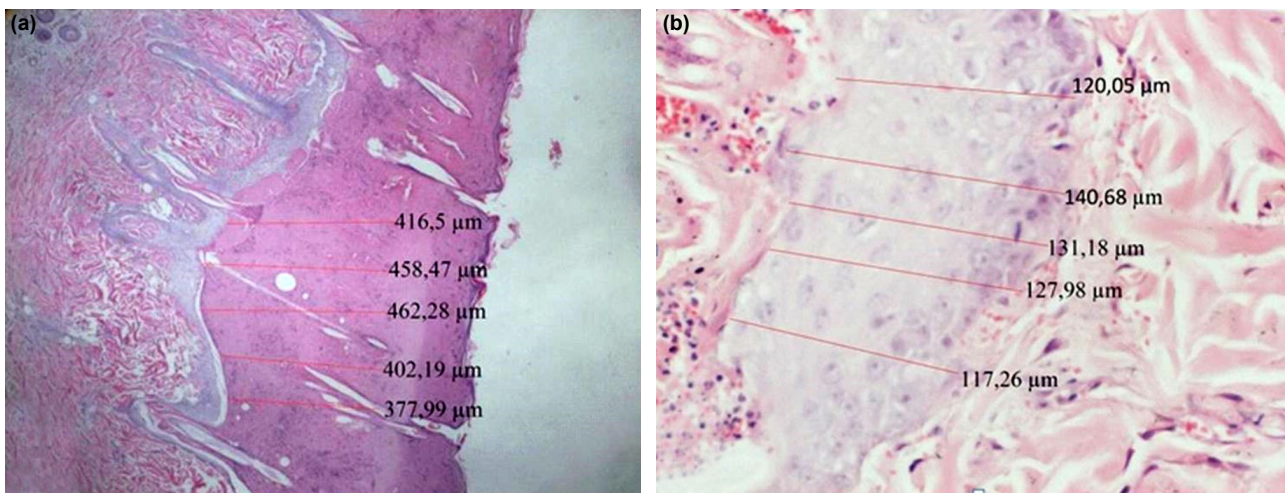

Figure 3. (a) Measurement of the zone of stasis from five different points. **(b)** Measurement of epithelium thickness from five different points.

ative if <10%, + (minimal) if 11 to 40%, ++ (mild) if 41 to 70%, and +++ (significant) if >71%.

Statistical Analysis

Data were examined using the Shapiro-Wilk test. To investigate the differences between the groups, the Kruskal-Wallis test was used for data outside of normal distribution; analysis of variance was used for data within the normal distribution. In the nonparametric test, subgroup analysis was performed using Mann-Whitney U test and interpreted with Bonferroni correction. P<0.05 was accepted as statistically significant. Data were evaluated using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Two rats in Group 3 died within 24 hours after burn induction, hence excluded from the study.

In the photo analysis performed using the ImageJ software program, no significant differences were found among the four groups concerning their average healed areas (Kruskal-Wallis=5.625, p=0.131), and no significant differences were noted in the biochemical analysis of hydroxyproline levels among the groups (p=0.614).

Table 1. Edema scores (Kruskal-Wallis Test)[a]

Group	n	Mean	Median (Min-Max)
Group 1 (Control)	10	2.00	2 (2–2)
Group 2 (ExM)	10	2.30	2 (2–3)
Group 3 (Px)	8	2.00	2 (2–2)
Group 4 (ExM+Px)	10	2.00	2 (2–2)

[a]Kruskal-Wallis Score = 8.880, p=0.031. Difference = Group 1 and Group 3 and Group 4 vs. Group 2. ExM: Exogenous melatonin; Px: Pinealectomy.

The histopathological and immunohistochemical analysis found significantly higher edema scoring in the ExM group vs. the other groups (p=0.031; Table 1; Fig. 4). Congestion scoring was significantly higher in the control group when compared with the ExM+Px group (p=0.031; Table 2; Fig. 5).

Fibrosis scoring was significantly higher in the ExM group than the other groups (p=0.011; Table 3; Fig. 6). No significant differences were noted among the groups concerning vascular proliferation and inflammatory infiltration.

The average thickness of the zone of stasis in the ExM group was significantly less than the other groups (p=0.009; Table

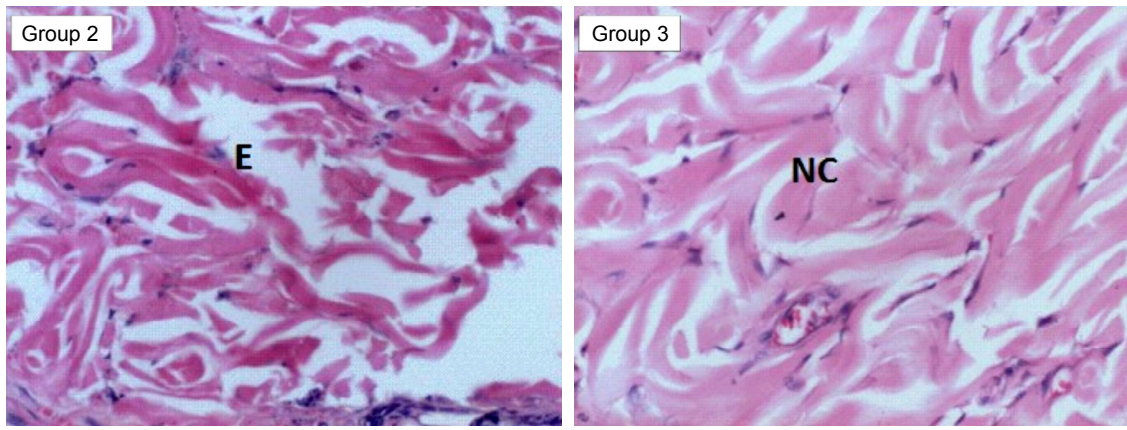

Figure 4. Comparison of edema shown in histopathological images of Groups 2 and 3: Edema is more significant in Group 2 (E). NC: collagen level is normal (Px) (H&Ex20).

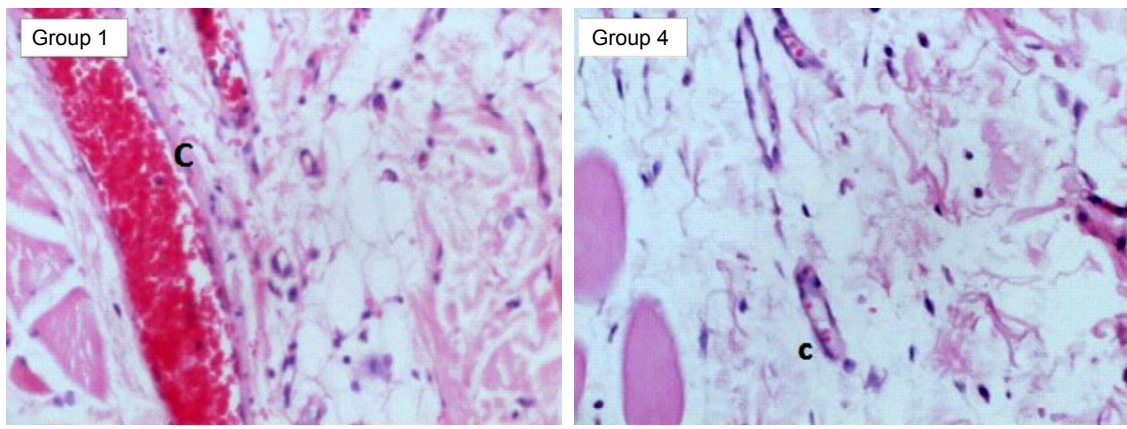

Figure 5. Congestion is higher in Group 1 (C) than Group 4 (c) (ExM+Px) (H&Ex20).

Table 2. Congestion scores (Kruskal-Wallis Test)[a]

Group	n	Mean	Median (Min-Max)
Group 1 (Control)	10	2.70	3 (2–3)
Group 2 (ExM)	10	2.40	2 (2–3)
Group 3 (Px)	8	2.38	2 (2–3)
Group 4 (ExM+Px)	10	2.00	2 (1–3)

[a]Kruskal-Wallis Score = 8.180, p=0.042. Difference = Group 1 and Group 4. ExM: Exogenous melatonin; Px: Pinealectomy.

Table 3. Fibrosis scores (Kruskal-Wallis Test)[a]

Group	n	Mean	Median (Min-Max)
Group 1 (Control)	10	2.20	2 (2–3)
Group 2 (ExM)	10	2.50	2.5 (2–3)
Group 3 (Px)	8	1.88	2 (1–2)
Group 4 (ExM+Px)	10	1.90	2 (1–2)

[a]Kruskal-Wallis Score = 11.142, p=0.011. Difference = Group 2 vs. Group 3 and Group 4ExM: Exogenous melatonin; Px: Pinealectomy.

Table 4. ZS thickness (ANOVA)[a]

Group	n	Mean	Median (Min-Max)
Group 1 (Control)	10	522.54	345.4–722.4
Group 2 (ExM)	10	521.30	340.8–903.4
Group 3 (Px)	8	574.45	463.2–673.4
Group 4 (ExM+Px)	10	700.12	493.0–960.4

[a]F=4.522, p=0.009, Difference = Group 1 and Group 2 vs. Group 4. ExM: Exogenous melatonin; Px: Pinealectomy; ZS: Zone of stasis.

Table 5. Type III collagen staining score (Kruskal-Wallis Test)[a]

Group	n	Mean	Median (Min-Max)
Group 1 (control)	10	1.20	1 (1–2)
Group 2 (ExM)	10	1.60	2 (1–2)
Group 3 (Px)	8	1.00	1 (1–1)
Group 4 (ExM+Px)	10	1.50	1.5 (1–2)

[a]Kruskal-Wallis Score = 8.880, p=0.031, Difference = Group 2 vs. Group 3. ExM: Exogenous melatonin; Px: Pinealectomy.

4). However, there were no significant differences among the groups concerning epithelium thickness.

The degree of type III collagen staining in the ExM group was significantly higher than the Px group (p=0.031; Table 5).

DISCUSSION

Burn injuries are a major source of physical and physiological trauma worldwide. If second-degree deep burn wounds are not treated promptly and appropriately, they may develop into full-thickness burns due to progressive tissue damage, leading to hypertrophic scars and contractures that require surgical excision and graft repair.[3] Tissue damage in the zone of stasis may be prevented with an appropriate treatment applied within two weeks from the initial injury.[8,9] Inflammation, ischemia and free oxygen radicals increase the progression of damage in burn wounds by affecting the viability of the zone of stasis.[10]

In our literature review, we identified several experimental studies that report their investigations on antioxidants' ability to prevent the progressive effects of free oxygen radicals in burn wounds. One study[11] reported that necrosis in the zone of stasis significantly reduced in groups treated with N-acetylcysteine than controls. Zor et al.,[12] based on nuclear imaging and autoradiography, reported that glutathione helped salvage the zone of stasis. Singer et al.[13] found that curcumin reduced the progression of burn injury in a rat comb burn model. Matsuda et al.[14] suggest that high-dose vitamin C would reduce edema in burn wounds in the porcine burn model, and superoxide dismutase has a salvaging effect on the zone of stasis.[15]

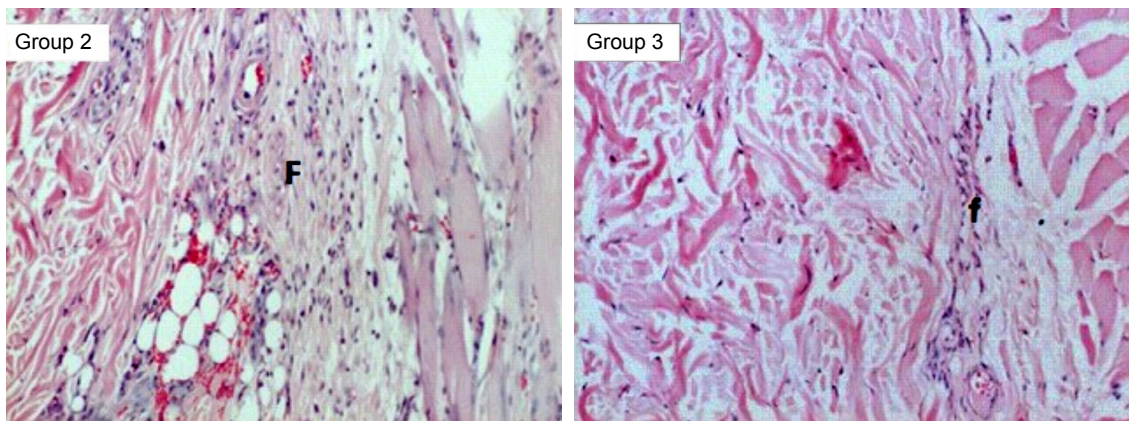

Figure 6. Fibrotic areas in Group 2 (F) are more significant (ExM) than Group 3 (f) (Px) (H&Ex20).

Melatonin's free oxygen radical scavenging ability is more effective than other antioxidants.[6] There are few studies that examine the effects of melatonin on burn healing. Most melatonin studies have focused on non-burn wound healing. Drobnik and Dabrowski[16] reported that pinealectomy enhanced collagen deposition in the skin, and melatonin application reduced the pinealectomy-induced elevation of collagen levels. Bulbuller et al.,[17] on the other hand, indicated that exogenous melatonin reduced collagen synthesis and epithelium proliferation and had negative effects on wound healing in both normal and pinealectomized rats. Contrary to Bulbuller et al.'s findings, we found the level of type III collagen staining to be significantly higher in the exogenous melatonin group than the pinealectomy group. Our finding suggests that melatonin, by enhancing the level of type III collagen in the burn wound, can decrease the likelihood of a hypertrophic scar and help burn wound healing since type III collagen deficiency increases scar formation.[18] In our study, fibrosis levels in the exogenous melatonin group were also significantly higher than the pinealectomy groups—a finding that showed the positive effect of melatonin on burn wound healing.

Kayapınar et al.[10] assessed melatonin's efficacy in saving the zone of stasis in rats. Kayapınar et al. divided their rats into two groups, a control group and a melatonin-treated group. Their study did not, however, assess the effects of pinealectomy on burn wound healing, nor did they analyze as many parameters as our study (e.g., collagen levels, epithelial thickness, and hydroxyproline levels). They found most of the interspaced areas to be alive in the melatonin-treated group. We found the thickness of the zone of stasis significantly less in our ExM group (the group with the highest total melatonin levels). Given the correlation between the zone of stasis and the depth of the wound; hence, the progress of the burn injury, this outcome proves that total melatonin levels have a profound impact on reducing the progression of burn injuries. Further supporting this, the ExM+Px group rats that could not produce endogenous melatonin presented with thicker zones of stasis and were administered exogenous melatonin. These findings demonstrate that total melatonin production, once exceeding a certain threshold, will exert a preventative effect on burn wound damage progression by reducing the zone of stasis.

Contrary to our findings, Kayapınar et al.[10] report higher edema levels in their controls than their melatonin-treated group. In our study, edema levels were higher in the ExM-treated group than controls, suggesting edema may be a side effect of higher melatonin levels. Although we administered exogenous melatonin in the ExM+Px group (Group 4), we found no differences in edema scoring than the control group (Group 1) and the Px group (Group 3). This finding may be due to the relatively low melatonin levels in these groups than the ExM group (Group 2).

The main goal during the recovery period is to minimize the burn wound area by contraction and extracellular matrix synthesis. Contraction of the wound surface area is a clinical indicator of healing. We found no significant differences among the groups concerning the average healed areas after seven days from the injury. We also noted similarities among the groups for epithelial thickness. Our study was designed to evaluate the early effects of melatonin on the healing of burn wounds in pinealectomized rats. A longer study is required to assess its macroscopic effects in the long-term.

Additionally, because hydroxyproline levels of all collagens in the dermis did not show any significant differences among the groups, hydroxyproline was deemed to be less meaningful than the level of type III.

Our study had several limitations. The first limitation was the short duration of seven days. Longer studies are needed to assess the effects of melatonin on wound healing macroscopically. While our study noted the early effects of melatonin burn wound healing, this study design did not allow for a longer-term evaluation of the effects of melatonin on burn wound healing.

While being a significant factor in the progression of burn wound injury, total melatonin levels above a certain threshold will reduce the zone of stasis and exert a preventative effect on burn wound damage progression. Additionally, melatonin may prevent the development of hypertrophic scarring by increasing fibrosis and type III collagen in burn wounds. The results of this study suggest that melatonin can be used as an additional, supplemental treatment in burn wound healing. Because our study aimed to evaluate the early effects of exogenous melatonin, further studies with higher doses administered over longer periods are warranted to assess its macroscopic effects on burn wound healing. A study of melatonin levels in serum or blood in each group would help determine an appropriate dosage of melatonin to affect burn wound healing. Despite promising experimental findings, future studies are needed to address three key areas: optimal dosages, administration timing and route of administration of exogenous melatonin for optimal outcomes in burn wound healing.

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Ethics Committee Approval: Ethics Committee Approval: This study was approved by Necmettin Erbakan University Experimental Medicine Research and Application Center Animal Experiments Ethics Committee (Date: 30.07.2012, Decision No: 2012/121518019).

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als: E.Ç.K.S.; Data: E.Ç.K.S.; Analysis: E.Ç.K.S., N.S.; Literature search: E.Ç.K.S.; Writing: E.Ç.K.S.; Critical revision: N.S.

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DENEYSEL ÇALIŞMA - *ÖZ*

Pinealektomize sıçanlarda melatoninin yanık yara iyileşmesine etkisi

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AMAÇ: Bu çalışmanın amacı, sıçanlarda melatoninin yanık yara iyileşmesine etkisini araştırmaktır.
GEREÇ VE YÖNTEM: Bu çalışmada 40 adet Wistar-albino cinsi deneysel erkek sıçanlar dört gruba ayrıldı: Grup 1; kontrol grubu, Grup 2; eksojen melatonin verilen grup, Grup 3; pinealektomi uygulanan grup ve Grup 4; pinealektomi yapıldıktan sonra eksojen melatonin uygulanan grup idi. Sıçanların sırtlarına kaynar suda bekletilmiş metal plak ile ikinci derece derin yanık oluşturuldu. Yedi gün boyunca yanık alanlarının iyileşmesi takip edildi. Yedi gün sonunda eksize edilen yanık alan dokularında hidroksiprolin, Tip 3 kollajen, ödem, iltihabi infiltrasyon, konjesyon, vasküler proliferasyon, fibrozis düzeyleri, staz zonu ve epitel kalınlıkları değerlendirildi.
BULGULAR: Staz zonu kalınlığı Grup 2'de diğer gruplara oranla daha azdı (p=0.009). Tip 3 kollajen boyanma (p=0.031), fibrozis (p=0.011) ve ödem (p=0.031) Grup 2'de diğer gruplara oranla daha fazlaydı. Konjesyon kontrol grubunda Grup 4'e göre daha fazlaydı (p=0.031). Değerlendirilen diğer parametrelerde, gruplar arasında anlamlı bir fark görülmedi.
TARTIŞMA: Bu çalışmada, total melatonin düzeyinin belli eşik düzeyi geçmesi durumunda, staz zonunu azaltarak yanık yara hasarının ilerlemesinde önleyici etkisi bulundu. Melatoninin, ayrıca hipertrofik skar gelişimini de önleyebildiği görüldü. Melatonin yanık yaralarında geleneksel tedaviyi destekleyebilecek potansiyel bir tedavi seçeneği olabilir. Bunun yanısıra, bu çalışmada belirtilen etkileri daha fazla değerlendirmek için daha uzun sürelerde ve daha yüksek dozlarda eksojen melatoninin uygulandığı çalışmalara ihtiyaç vardır.
Anahtar sözcükler: Eksojen melatonin; endojen melatonin; pinealektomi; yanık; yara.

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