Effects of Copper (II) Albumin Complex on Thermal Skin Burn

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ABSTRACT

Background: *Thermal burn results in release of many chemical mediators such as free radicals, biogenic amines and neurotransmitters. The modulations of these mediators can enhance burn wound healing.*

Aim of the Work: *To evaluate effects of copper (II) albumin complex on thermal wound healing.*

Materials and Methods: *An animal model of 190 Sprague Dawely rats was established. Ten rats served as a control group and 180 rats were exposed to 10% total body surface area full thickness thermal burn. The rats were equally divided into three groups and treated topically either with soft paraffin, moist exposed burn ointment (MEBO), or with copper (II) albumin complex. At 4 hours, first day, third day, first week, second week and third week post-injury, plasma was used for determination of malondialdehyde (MDA), total antioxidant capacity (TAC), 5-hydroxy tryptamine (5-HT) and gamma amino butyric acid (GABA). Skin tissues were taken for histopathological examination with light microscopy.*

Results: *Thermal injury resulted in a significant increase of plasma levels of MDA, 5-HT and GABA and a significant decrease of TAC. The treated groups with copper (II) albumin complex and MEBO showed a significant decrease of plasma levels of MDA and 5-HT and a significant increase of plasma levels of TAC. Copper (II) albumin complex treatment was associated with a significant increase of plasma levels of GABA at the first and third day post-burn as compared to the other treated groups. Characteristic enhancement of regeneration of epidermis and hair follicles was observed following application of copper (II) albumin complex.*

Conclusions: *The topical application of copper (II) albumin complex was associated with improved healing signs of full thickness thermal burn due to its antioxidant, anti-inflammatory and pain modulating effects.*

Keywords: *thermal burn, copper (II) albumin complex, MEBO*

INTRODUCTION

Burns are disabling injuries affect all ages and are associated with many problems for patients. Flame and scalds are the most common etiologies[(1)]. Burn produces local proinflammatory mediators which result in edema, wound inflammation and systemic inflammatory syndrome[(2)]. Many studies have shown that oxygen-derived free radicals participate in the pathogenesis of burn tissue damage [(3)]. Release of reactive oxygen species (ROS) in affected tissues results in initiation of lipid peroxidation in burned skin and distant organs[(4)]. ROS, such as superoxide radical, hydroxyl radical and hydrogen peroxide induce tissue damage through peroxidation of lipids, oxidation of protein, and disruption of DNA strands[(5)]. On that base, many antioxidant supplements are used in treatment of burn wound such as α-tocopherol[(6)] and vitamin C[(7)].

Following burn injury, a localized and widespread neuroinflammatory process occurs that includes mast cell degranulation, and release of bioamines such as 5-Hydroxytryptamine (5-HT), bradykinin, prostaglandins and nerve growth factors[(8)]. 5-HT is an important mediator of the vascular effects of burns in humans resulting in burn edema[(9)]. The increased vascular permeability seen after burn interferes with organ function and healing process.

Uncontrolled burn pain results in release of toxic products and depression of the immunological system [(10)]. Reduction of burn pain is a significant sign of healing. GABA plays important role in normal and pathological processes in the skin; it stimulates barrier recovery of the mouse skin[(11)]. The presynaptic inhibition of GABA neurons by ROS could be an underlying mechanism of neuropathic pain [(12)].

There are many treatment options of burn wounds, including surgical debridement of burned skin and the use of antioxidants [(13)]. MEBO is an ointment consisting of an oily base of sesame oil and bees wax with herbal components comprised of 18 amino acids, 4 fatty acids, 7 polysaccharides, vitamins, and trace elements as copper, plus an active substance consisting of 0.25%, β-sitosterol [(14)]. MEBO provides wound healing in a moist environment and assists cellular proliferation through β sitosterol action [(15)]. MEBO is widely used as a powerful treating agent of burn wounds, especially partial thickness burn [(16)].

Copper complexes were used as anti inflammatory agents in induced rheumatoid arthritis[(17)] and non alcoholic fatty degeneration of liver[(18)]. They can act mostly by changing oxidants/ antioxidants properties and scavenging the toxic oxygen species[(19)]. Copper nicotinate

complex had curable effect in full thickness experimental scald burn in rats through anti-inflammatory antioxidant effect [20].

The present work has been designed to investigate the possible effect(s) of the copper (II) albumin complex as an anti-inflammatory and antioxidant agent for promoting experimental burn wound healing

MATERIALS & METHODS

All the procedures were performed in accordance with the Assiut University guidelines for care and use of laboratory animals.

Rats and injuries:

An animal model of 190 Sprague-Dawely rats of about 100-120 grams body weight was established. Ten rats served as a control group. 180 rats were subjected to brief ether anesthesia and exposed to 10% total body surface area full thickness thermal burn as described by **Santos et al.**[21]. The rats were equally divided into three groups and treated topically either with soft paraffin, moist exposed burn ointment (MEBO), or with copper (II) albumin complex suspended into soft paraffin. Ten rats from each group were sacrificed at 4 hour, first day, third day, one week, two weeks and three weeks from the beginning of burn induction. Blood and skin tissue samples were collected for biochemical and histological examinations.

Biochemical measurements:

Malondialdehyde (MDA) was measured by using kit supplied by diagnostics, Egypt; according to the method described by **Satoh** [22]. The total antioxidant capacity (TAC) was measured using kit supplied by diagnostics, Egypt; according to the method described by **Koracevic et al.,**[23]. 5-Hydroxy tryptamine (5-HT) was determined by fluorometric method as described by **Curzon and Green**[24] as modified by **Curzon et al.,** [25]. 5-HT forms highly fluorescent complex with O-phthalaldehyde, the addition of L -cysteine to the reaction mixture improves the sensitivity of the method. GABA was determined by fluorometric method[26], where it reacts with ninhydrin and glutamic acid producing fluorescent product.

Histological examinations:

Skin tissue samples were fixed in 10% neutral buffered formalin solution, embedded in paraffin wax, cut into 5 μm-thick sections and stained with hematoxylin and eosin (H&E) for examination by light microscope.

Statistical analysis: One way analysis of variance (ANOVA) is used to compare between all groups followed by student's unpaired t-test to compare between any two groups

RESULTS

Four hours post burn injury plasma levels of MDA was significantly increased as compared to

control group. Paraffin treated group showed an increase of plasma MDA level that continued to the third week as compared to the control group. MEBO and Copper (II) albumin complex treated groups had lower MDA level than paraffin treated group reaching gradually the control level at third week. A summary of these results is shown in table (1). TAC plasma levels were significantly decreased after burn injury as compared with control group. MEBO and copper (II) albumin complex treated group showed significant increase in the plasma TAC to reach to near normal level at the third week of treatment. A summary of these results is shown in table (2). 5-HT plasma levels were increased at the 4 h, 24 h and 72 h post-burn then decreased reaching control level at the first week in the three treated groups as compared to control group. MEBO and Copper (II) albumin treated groups had lower levels at 24 h and 72 h as compared to control group. A summary of these results is shown in table (3). GABA plasma level was significantly increased post-burn injury in the three treated groups until the third week as compared to control group. Copper (II) albumin treatment was associated with significant increase at 24 h and 72 h post burn as compared to paraffin. A summary of these results is shown in table (4).

Histopathological examinations of skin sections of burned skin tissues are shown in figure (1). 24 hours after thermal burn, skin sections showed extensive necrosis and degeneration with complete destruction of epidermis, dermis, hair follicles and hypodermis figure (1A). Third week post-burn paraffin treated skin showed (unremarkable) disorganized epidermis and hair follicles (figure 1B). MEBO treated skin showed re-epithelization of the epidermis and regenerating hair follicles (figure 1C). Copper (II) albumin treated skin showed regenerated epidermis keratin horns and hair follicle attained normal structure (figure 1D).

Table (1): plasma MDA values (nmol /ml) in control, Paraffin, MEBO and Copper complex treated groups

parameter	Control (n=10)	paraffin treated Group (n = 10)						MEBO treated group (n = 10)						Copper albumin complex treated group (n = 10)					
		4h	24h	72h	1st Wee	2nd week	3rd week	4h	24h	72h	1st week	2nd week	3rd week	4h	24h	72h	1st week	2nd week	3rd week
MDA (nmol/ml)	1.27 ± 0.18	3.12 ± 0.25	3.60 ± 0.20	5.20 ± 0.30	3.30 ± 0.20	2.70 ± 0.40	2.40 ± 0.20	2.56 ± 0.23	3.40 ± 0.20	4.10 ± 0.60	2.40 ± 0.20	2.03 ± 0.30	1.40 ± 0.10	2.90 ± 0.04	3.50 ± 0.30	4.10 ± 0.10	2.20 ± 0.20	2.05 ± 0.20	1.49 ± 0.02
P1		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.05	<0.001	<0.001	NS	<0.001	<0.001	<0.001	<0.001	<0.001	NS
P2		–	–	–	–	–	–	<0.001	NS	<0.001	<0.001	<0.001	<0.001	NS	NS	<0.001	<0.001	<0.001	<0.001

Table (2): plasma TAC levels (µM/L) in Control, Paraffin, MEBO and Copper (II) albumin complex treated groups

parameter	Control (n=10)	paraffin treated Group (n = 10)						MEBO treated group (n = 10)						Copper albumin complex treated group (n = 10)					
		4h	24h	72h	1st week	2nd week	3rd week	4h	24h	72h	1st week	2nd week	3rd week	4h	24h	72h	1st week	2nd week	3rd week
TAC (µM/L)	0.61± 0.03	0.51 *± 0.04	0.42 *± 0.03	0.33 *± 0.04	0.45±* 0.01	0.51 *± 0.04	0.56 *± 0.02	0.53± 0.04	0.44± 0.02	0.34± 0.02	0.52± 0.03	0.54± 0.01	0.58± 0.02	0.54± 0.04	0.44± 0.03	0.35± 0.03	0.54± 0.01	0.56± 0.07	0.59± 0.03
P1		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	NS	<0.001	<0.001	<0.001	<0.001	<0.05	NS
P2		–	–	–	–	–	–	NS	NS	NS	<0.001	<0.05	<0.05	NS	NS	NS	<0.001	<0.05	<0.01

P1: versus control group, .p2: versusparaffin treated group .NS: non significant. Data are expressed as mean± SD

Table (3): 5-HT plasma levels (ng/ml) in Control, Paraffin, MEBO and Copper (II) albumin complex treated groups

parameter	Control (n=10)	Paraffin treated Group (n = 10)						MEBO treated group (n = 10)						Copper albumin complex treated group (n = 10)					
		4h	24h	72h	1st week	2nd week	3rd week	4h	24h	72h	1st week	2nd week	3rd week	4h	24h	72h	1st week	2nd week	3rd week
5-HT (ng/ml)	256.3 ± 48.7	346.6 ± 22.5	391.1 ± 17.8	459 ± 23.1	2749± 65	2853 ± 44.2	2619± 37.9	329 ± 25	330 ± 31.6	336 ± 14.3	2545 ± 24.4	288 ± 20	248 ± 38.9	321.9 ± 19.4	350 ± 35.4	378.5 ± 14	2655 ± 45.9	286 ± 16.5	252 ± 36
P1		<0.001	<0.001	<0.001	NS	NS	NS	<0.05	<0.05	<0.05	NS	NS	NS	<0.01	<0.05	<0.01	NS	NS	NS
P2		–	–	–	–	–	–	NS	<0.01	<0.001	NS	NS	NS	<0.05	<0.05	<0.01	NS	NS	NS

Table (4): GABA plasma levels (µg/ml) in Control, Paraffin, MEBO and Copper (II) albumin complex treated groups

parameter	Control (n=10)	paraffin treated Group (n = 60)						MEBO treated group (n = 60)						Copper albumin complex treated group (n = 60)					
		4h	24h	72h	1st week	2nd week	3rd week	4h	24h	72h	1st week	2nd week	3rd week	4h	24h	72h	1st week	2nd week	3rd week
GABA (µg/ml)	1.30± 0.02	2.06 ± 0.2	1.86± 0.1	2.21± 0.2	2.35 ± 0.47	2.20± 0.29	2.4± 0.60	2.22± 0.13	2.09± 0.20	2.12± 0.20	2.16± 0.40	1.8± 0.20	2.08± 0.50	2.08± 0.20	2.31± 0.12	2.84± 0.20	2.90± 0.40	2.63± 0.60	2.13± 0.30
P1		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
P2		–	–	–	–	–	–	NS	<0.01	NS	NS	<0.001	NS	NS	<0.001	<0.001	NS	NS	NS

P1: versus control group, .p2: versusparaffin treated group .NS: non significant. Data are expressed as mean± SD

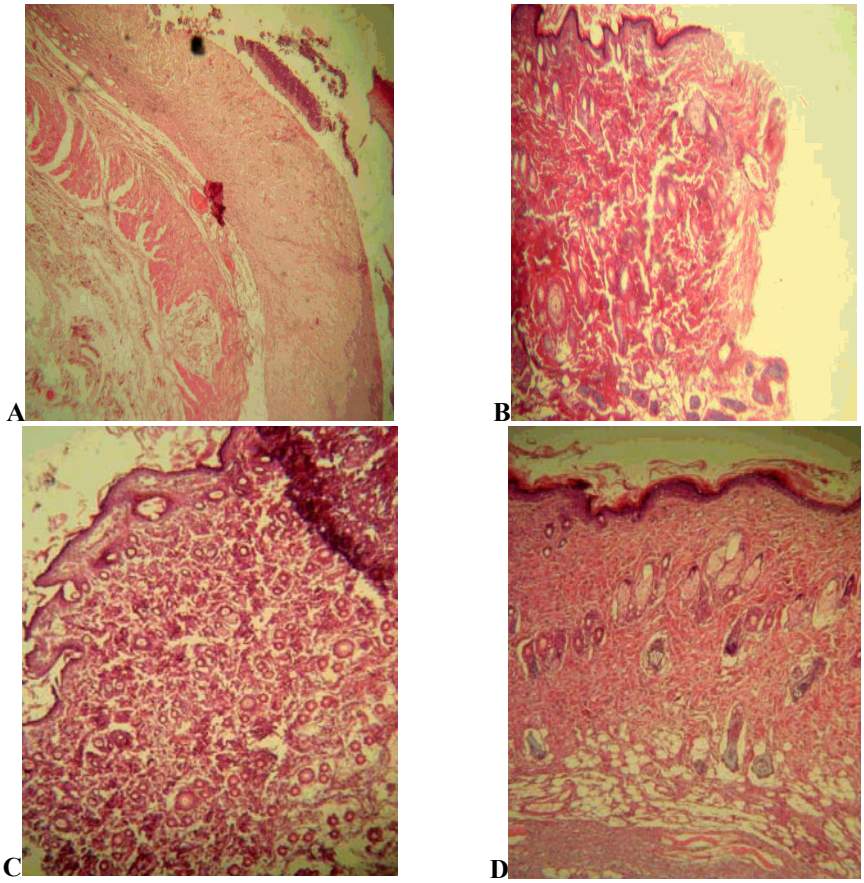

Figure (1): Histopathological changes following thermal burn. (A):24 hour post burn skin tissue shows destruction of epidermis, dermis and hair follicles (H&E X100). (B): Control treated skin shows disorganized hair follicles and epidermis (H&E X100). (C): MEBO treated skin shows regenerating epidermis and hair follicles (H&EX100). (D): Copper (II) albumin complex treated skin shows epidermis with keratin horny layer and regenerating hair follicle (H&E X100).

DISCUSSION

During thermal burn reactive oxygen species (ROS) are produced exposing all tissues to oxidative injury[27]. In the present study plasma MDA levels were increased significantly following thermal injury as compared to control. This result is consistent with many experimental and clinical studies which had shown that oxygen-derived free radicals rise in the plasma after thermal injury and that rise can be evident one hour post-injury in serum[28,29]. High plasma level of MDA in burned rats was

returned back near the normal level at the third week of treatment with copper (II) albumin complex and MEBO; this finding can be paid to the antioxidant activity of copper (II) albumin complex. **Firat et al.** [30] suggested that antioxidant drugs may prevent neutrophil-dependent tissue damage and burn-induced oxidative injury.

As regard the mean plasma levels of total antioxidant capacity, the scald injury reduced significantly the total antioxidant capacity as compared with control group. TAC is a sensitive marker of oxidative stress, maintaining low levels throughout the burn with high levels of lipid peroxidation products; this was attributed to oxygen free radicals [31]. The total antioxidant plasma levels were gradually increased reaching the control level in copper complex group and MEBO group while not in paraffin treated group at third week of treatment. Copper complexes can increase superoxide dismutase enzyme (SOD) activity, leading to relief of oxidative stress [32, 33].

In the current study plasma levels of 5-HT were increased at the first seventy two hour post-burn when compared with control group. Circulating platelets react with exposed collagen, adhere and aggregate and release their content including serotonin [34]. These results are in accordance with **Samuelsson et al.** [35] study. The authors reported that 5-HT was increased in blood and urine during the early phase of the burn. MEBO and copper complex treated groups showed significant decrease in 5-HT plasma levels in the first seventy two hours post-burn as compared with paraffin treated group. This result could be attributed to inhibition of platelets aggregation and cyclooxygenase [36].

Reichl et al., [37] demonstrated that GABAA and GABAB receptors are involved in mediation of mechanical and thermal hyperalgesia after incision wound. In the present study plasma levels of GABA were increased following thermal burn as compared with control group. Copper (II) albumin complex treatment was associated with significant increase of GABA plasma levels at the twenty four hours and at seventy two hours post-burn as compared to paraffin and MEBO treated groups. This action can help in reduction of pain sensation due to decrease in the inflammatory response and decrease of ROS [38]. Reactive oxygen species in the spinal dorsal horn could cause neuropathic pain that result from nerve injury or inflammatory insult [39]. Inhibition of GABA neurons by ROS in the spinal dorsal horn could be a mechanism explaining neuropathic pain[12]. Copper complexes have potent analgesic effect in inflammatory model of pain [40].

In our study Copper (II) albumin complex treatment was associated with enhancement of epidermal repithelization and hair follicles regeneration. **Shubina and Shatalin**[41] demonstrated that taxifolin and its complexes with iron and copper ions resulted in a more effective skin regeneration and repair of hair follicles due to utilization of toxic metabolites and lipid peroxidation products in chemical burn.

CONCLUSION

Copper (II) albumin complex treatment improved healing of full thickness burn. It reduced MDA and increased TAC by antioxidant action. Anti-inflammatory action of that complex resulted in decreased 5-HT. As pain modulating agent it increased GABA level.

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تأثير معقد النحاس الثنائى مع الألبيومين على الحروق المحدثة حراريا

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الحروق الناتجة عن الحرارة فوق الاحتمال الفسيولوجي تعد من أخطر الاصابات وتؤدى الي تغيرات بيوكيميائية فى الجلد والانسجة الاخرى تنتهي باطلاق الجذورالبيوكيميائية الشاردة والعديد من الموصلات العصبية ويعتبر الألم الناتج عن الحروق من الالام التى تتطلب الرعاية االعلاجية. تمت هده الدراسة باستحداث حرق جلدى بعمق كامل في مئة وثمانين من فئران التجارب التي قسمت الى ثلاث مجموعات علاجية .المجموعة الاولي عولجت باستخدام الفازلين الطبى وشملت ستين فأرا. المجموعة الثانية عولجت باستخدام عقار الميبو وشملت ستين فأرا. المجموعة الثالثة عولجت باستخدام معقد النحاس الثنائى مع الألبيومين وشملت ستون فأرا. استخدمت عشرة فئران سليمة كمجموعة ضابطة. وقد ابتدأ العلاج بعد الحرق مباشرة واستمر لمدة ثلاث أسابيع. تم التضحية بعشرة فئران من كل مجموعة علاجية عند أربعة ، واربع وعشرون ، واثنان وسبعون ساعة ، والأسبوع الأول ، والثاني ، والثالث من بداية العلاج ، وقد تم أخذ عينات من الجلد المصاب وتمت دراستها هستولوجيا. وقد تم أخذ البلازما لقياس كلا من ثنائى ألدهيد المالون ، ومجموع القدرات المضادة للأكسدة ، وخمسة هيدروكسى تريبتامين ، وحمض الجاما امينو بيوتريك. ووجد ان كلا من ثنائى ألدهيد المالون ، وخمسة هيدروكسى تريبتا مين ، و حمض الجاما امينو بيوتريك قد ارتفع مستواها فى البلازما وانخفض مستوى مجموع القدرات المضادة للأكسدة بعد حدوث الحرق. ووجد ان العلاج باستخدام معقد النحاس الثنائى مع الألبيومين وعقار الميبو ادى ا لي شفاء ملحوظ على المستوي الهستولوجي و زيادة فى مستوي مجموع القدرات المضادة للأكسدة و حمض الجاما أمينو بيوتريك وانخفاض في ثنائى ألدهيد المالون ، وخمسة هيدروكسى تريبتا مين مقارنة باستخدام الفازلين الطبى. من هده النتائج يمكن الاستنتاج ان معقد النحاس الثنائى مع الألبيومين له تأثير على شفاء الحروق في الفئران.