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Mini-Review

ANTIOXIDANTS SUPPLEMENTATION BASED ON NATURAL PRODUCTS IN THE TREATMENT OF THE THERMAL SKIN INJURY

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Abstract. *Thermal injuries are a major medical, economic and social problem, whose severity, morbidity, mortality, prognosis and treatment outcome directly depend on the surface and depth of the burn, but also on the patient's age, health status and accompanying complications. The treatment of thermal injury is long and complex, and the outcome is often uncertain with a very complex rehabilitation process, because the injury damages both physical and psychological health. Constant innovations in the protocol of medical treatment and the search for new mechanisms involved in the pathogenesis of burns can be helpful in successful treatment. Therefore, there is a constant search for adjuvant therapies that will improve results like HBO, AO, platelet- rich plasma, negative pressure wound therapy and others. In recent years, the application of antioxidants as adjuvant therapy for the care and treatment of wounds has been the subject of various researche. Antioxidants are biologically active molecules that prevent the creation of free radicals in the body and at the same time neutralize the existing ones, this way participating in maintaining the oxidative status at the desired level. Antioxidant -rich natural products may provide a solution to improve wound healing. The application of antioxidant therapy has shown numerous benefits in improving the outcome of burns. However, more information is needed from the clinical trials on the use of natural products, especially in combination with other therapies.*

Key words: *thermal skin injury, hyperbaric oxygen therapy, antioxidant -rich natural products*

Introduction

Thermal injuries of the skin occur due to the effect of excessive heat. Depending on the nature of the heating agent, its temperature and length of exposure, the superficial layers of the skin are primarily damaged, and with more intense impacts, deeper structures are affected [1]. The heat source can be electricity, chemical substances, radiation, flame, hot surface, liquid or steam [2]. According to the World Health Organization more than 11 million burns occur annually, majority taking place in the underdeveloped and the developing countries due to older buildings, lower safety standards, absence of smoke detectors, faulty electricity and others. Burns can vary from small wounds that are treated on an outpatient basis to very large injuries that are treated in specialized centers and lead to multiorgan system failure, long stays in hospitals and other functional and psychosocial consequences. Approximately 6.5 percent of all burn victims are treated in specialized burn centers, with an overall mortality rate of 3% [2, 3]. Burns affect a wide range of patients with different mechanisms of damage, depth and localization of the burn. The degree of damage depends on the strength of the heat source, the length of the heat effect, the method of injury, the age of the patient, the location of the burn and the patient's health condition. Burn injuries affect both the young and old, women and men. In adults, male persons most often get burns outside the home, outdoors and at the workplace, and female persons, at home, usually while cooking food [3]. Children usually get burns at home, when they are not under the supervision of adults. Based on data from the American Burn Association, burns are more common in men. Burn injuries represent an important public health issue and a serious pathology that leads to serious morbidity and mortality, but also has a large health economic impact. Between 7 and 12 million people who sustain burn injuries and require medical treatment are absent from school or work for longer periods of time [3, 4]. The incidence of burn injuries is higher than that of human immunodeficiency virus and tuberculosis combined and is near the incidence of all malignant neoplasms [4]. Burn injuries represent one of the most common injuries in the world, of which more than 86% are thermal injuries and they are caused by flame, hot liquid or steam, as well as contact with a hot object. About 4% of burns are caused by electricity, 3% by chemical substances, and 7% are other types of burns [5]. According to data from the Global Burden of Disease project, run by the Institute for Health Metrics and Evaluation in cooperation with the World Health Organization where 204 countries were involved, almost 8,5 million burns caused by flame, heat or hot substance were recorded in 2019. More than 100 thousand ended in death, most of which were concentrated in the

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age of 1–4 years. The study showed that the number of new cases of burns is increasing globally, but with a continuous decrease in deaths [6]. Approximately 2 million people in the USA are injured every year [7]. Thermal injuries are the fourth leading cause of trauma and death in adults, and second in order for children aged 1 to 4 years [8, 9]. Even after recovery, thermal injuries are a serious problem, because in addition to physical damage, they also lead to psychological damage, such as trauma and stress, which are often caused by long hospital stays, scars, and permanent disability [10]. Between 7 and 12 million people who sustain burn injuries and require medical treatment are absent from school or work for longer periods of time [11]. Returning to work or school is the important outcome after burn trauma, as work is not only a source of income but also evidence of integration and participation in the community. A European study showed that the average number of days off work after burn trauma was close to 60, which speaks to the high economic burden that burn trauma causes. Survival after severe burns has increased significantly due to better treatment of burn shock, more active surgical approach, more effective infection control, immune and metabolic status. However, burns continue to be of great medical, scientific and economic importance and can affect and worsen the physical and mental health of survivors and present significant societal challenges, especially for those with more extensive burns [12, 13].

Thermal injuries can be classified according to a number of factors, including their depth, etiology and percentage of body surface area affected. All these factors together determine the degree of burn injury. Thermal injuries can be caused by: hot liquids, which is the most common type, accounting for nearly 70% of burns in children, but also common in the elderly; dry heat injuries, usually caused by direct contact with a flame or radiant heat and contact injuries which arise in direct contact with a hot object [14]. The division of burns depending on the depth of skin largely determines the possibility of healing and the need for surgical interventions. We distinguish superficial, first-degree burns, which involve only the epidermis, partial thickness or second-degree burns, which are further divided into superficial, which involve the papillary dermis and deep partial-thickness burns that extend into the reticular dermis, and full-thickness burns or third-degree burns, which extend through the entire thickness of the skin. Fourth degree burns, in addition to the entire skin, also affect the basic structures [15]. One of the leading things in assessing the severity of an injury is determining the area of the body affected by the burn, and the ability to calculate the burned area is very important for doctors. Several methods have been accepted around the world for determining the area affected by burns [16]. A crucial factor in the treatment of burns is localization. Burns on the face, hands, feet and genitals, as well as large burns on other parts of the body, are treated in burn centers [17]. According to the severity of the clinical picture, we distinguish mild, medium and severe thermal injuries. The most important, but not the only, elements in that determination are the size, depth and extent of the injury. We determine the size and scope of the injury as a percentage of the damaged skin in relation to the total skin surface (TBSA – total body surface). In clinical practice, the "rule of nine" and "palm rule" are most often used for basic orientation [18].

All of the above provides general guidelines for the choice of treatment for injured patients. The biggest challenge in the treatment is the most severe burns [19].

Materials and Methods

Through a systematic literature review and analysis of published professional and scientific works in medical journals (Google Scholar, SCIndex, PubMed), as well as available books, we collected the data that we present in this paper.

Results and Discussion

The treatment of thermal injury is long and complex, and the outcome is often uncertain with a very complex rehabilitation process, because the injury damages both physical and psychological health. Severe burns represent a major problem and require a multidisciplinary approach of medical workers, lot of drugs and other pharmaceutical products [20]. Surgical and pharmacological strategies must be adequately coordinated and adapted to the different pathophysiological stages of the injury [21]. The first 24 hours of intensive treatment are focused on fluid replacement, pain control and preventing the development of complications such as infections. Once the patient has been stabilized, the wound is evaluated. In relation to the exact depth of the burn wound the surgeon must decide whether to proceed with conservative or operative treatment [22]. After the end of the acute treatment of burns, there is a proliferation of dermal tissue, which may lead to significant damage to the integrity of the skin and, consequently, to hypertrophic scarring. They can persist for a longer period of time after the end of the treatment and together with the resulting contractures are a common cause of morbidity and loss of function. If the localization of the burn is in the area of the joints, the resulting contracture can lead to limitation of movement in the joint, deformity and eventually disability which will result in a longer absence from work and a more difficult return to daily activities. If the contractures involve the legs, there may be difficulty in squatting, sitting or walking. If they are localized on the trunk and arms, they can lead to difficulties in dressing, bathing and working with the hands. Contractures in the mouth and neck can lead to deformity of the jaw, which results in difficult communication and difficult food intake [12]. All of the above indicates functional damage, however, the psychological impact on the patient's health is also very important. A long stay in the hospital, intense pain, loss of function, fear of the reaction of the environment, the struggle to accept a new way of lif' and many other factors lead to different emotional rea'tions in a burned patient, and they represent a vulnerable population [22],

By popularizing the application of early excision of burns in the sixties and seventies years of the last century extensive burn care has improved. Cases of survival have been recorded even after 95% TBSA burns [23]. Early excision removes all dead tissue, reduces mortality and morbidity, and also reduces the possibility of infection [24]. Autograft is ideal for covering a burn wound, but in more severe burns where there is not always free donor skin, allograft is used temporarily [25]. In minor burns, donor sites for autografts are not a problem unless the patient has associated comorbidities [26]. Using early excision of burns by any technique, greater survival has been reported in the treatment of children with severe burns [27]. Despite advances in the treatment and care of burn patients, they are still a major cause of morbidity and mortality. Constant innovations in the protocol of medical treatment and the search for new mechanisms involved in the pathogenesis of burns can be helpful in successful treatment. New therapeutic approaches are emerging that address scarring, mental health, and quality of life. New forms of treatment have the effect of improving the outcome of burns both acutely and in the long term. Shorter duration of sick leave and return to work are important outcomes after burn trauma. Approximately 21–50% of patients experience some type of occupational difficulty due to the burn after returning to work. Estimates of the percentage of burn patients who are not fully able to return to work after injury vary widely, from less than 1% to 15% [28]. New therapeutic protocols that have been shown to significantly promote faster healing of wounds and reduce the frequency of infections, there by shortening the hospital stay and enabling a faster return to work, are becoming very important in the treatment of burns, because they also affect their psychosocial consequences [29]. There is a constant search for adjuvant therapies that will improve results like HBO, AO, platelet rich plasma, negative pressure wound therapy and others [30].

Hyperbaric therapy is an adjuvant therapy proposed in 1965. To improve the outcome of thermal burns. It represents the application of 100% oxygen pressure greater than 1 atmosphere, and works by increasing the oxygen pressure so that it can diffuse directly into the various tissues. The effects of increased oxygen supply are angiogenesis, increased proliferation of fibroblasts and reduction of tissue edema. By increasing the oxygen supply, the oxygen-deprived tissue surrounding the burn site can be restored to normal levels [31]. Studies on the treatment of burns in animals using HBO therapy have shown that the application of the therapy reduces edema through vasoconstriction and stimulates the distribution of oxygen through direct osmotic action [31]. A human study demonstrated the potential benefit of HBO as an adjunctive therapy in the treatment of burns [32]. Studies have shown that the use of HBO therapy reduces the frequency of wound infection, leads to faster healing, reduces mortality, the length of hospital stay and the need for surgery, and also enables longer maintenance of skin grafts [33, 34].

In recent years, application of antioxidants as an adjuvant therapy for the care and treatment of wounds has been the subject of various researches [35, 36]. Thermal injury leads to damage of the physical barrier of the skin which normally participates in protecting the body from microorganismus and causes an immunocompromised state that predispose burn patients to infection, sepsis and multi organ disfunction [37]. In addition to local tissue damage, the traumatic condition caused by thermal injury also leads to systemic changes. There is a disturbance in the balance between free radicals and the body's natural cleansers, primarily due to increased activity of free radicals and lipid peroxidation [38]. The use of antioxidants has a positive effect on immune function, which can reduce the incidence of wound infection and other complications in burn patients [37]. Antioxidants are biologically active molecules that prevent the creation of free radicals in the body and at the same time neutralize the existing ones, thus participating in maintaining the oxidative status at the desired level [39]. As thermal skin injury is an oxidative process associated with biological and metabolic changes, this emphasizes the importance of therapeutic targeting of oxidative stress in the treatment of burns [37, 38]. Numerous studies report the stimulating effect of antioxidants on wound healing processes [37, 40–42]. The reduction of levels of oxidative stress leads to reduced inflammation and hypermetabolism, improving clinical outcomes [34]. Most studies have shown that the use of antioxidants leads to a reduction in the time required for wound healing. It has also been shown that the duration of hospitalization and the incidence of infection are reduced with the use of antioxidants [37, 38].

There are several classifications of antioxidants. The main divisions are based on their mechanism of action, origin, how they are applied to the human body, chemical nature of the molecule and solubility. Based on their origin and chemical nature, antioxidants are divided into natural and synthetic. Natural antioxidants are compounds obtained from plants and other living things organisms with a strong potential to inhibit oxidative stress by controlling the formation of free radicals, scavenging the free radicals, interrupting the free radical-mediated chain reactions, and preventing the lipid peroxidation process. The natural antioxidants frequently cited in literature pertaining to nutrition and wound healing include: Vitamin E, alpha-lipoic acid, vitamin C, grape extract, coenzyme Q10, glutathione, and lutein, all of which promote the development of new tissue in wounds by reducing the concentration of free radicals [35]. Vitamin E is one of the most common lipid-soluble antioxidants used to combat the harmful effects of free radicals in the skin. Vitamin E has increased effectiveness in wound healing due its natural ability to penetrate skin very easily [42]. Several studies monitored the level of malondialdehyde, which is one of the end products of the peroxidation of polyunsaturated fatty acids and a marker of oxidative stress, after the application of natural antioxidants. A randomized study conducted on 36 children admitted to a burn unit showed a significant reduction in MDA

levels in patients who were supplemented with the vitamin E, C and zinc sulfate. A study conducted in 35 severely burned patients also showed a reduction in lipid peroxidation markers in 18 patients who recived vitamin E [41, 42]. A study that included 180 patients of both sexes of different ages with burns of different percentages clearly demonstrated the beneficial effect of natural antioxidants (vitamins E and C, zinc sulfate, allopurinol, melatonin and N-acetylcysteine) in the treatment of burn patients, where we particularly focus on the positive effect of zinc sulfate. The results show that the application of zinc sulfate reduced the mortality rate and shortened the healing time of wounds. A study with a smaller number of patients conducted by Al-Kaisy et al showed similar results. Table 1 [37, 43].

Table 1 Application of zinc sulfate in burned patients

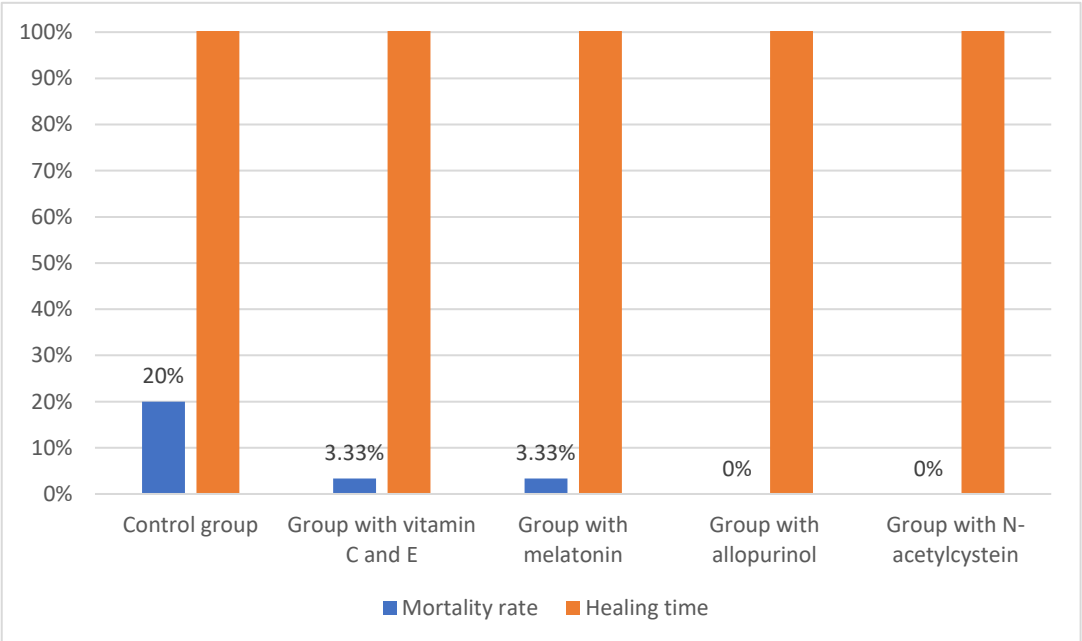
	Mortality rate	Healing time
Control group	20%	20 ± 2,4
Group with zinc sulphate	3.33%	10 ± 2,1
Control group	7,0%	9,2 ± 1,6
Group with zinc sulphate	-	8,6 ± 2,2

In addition to zinc sulfate, the application of other antioxidants also showed positive results in reducing wound healing time and mortality which is shown by the results in graph 1 where we can see that the mortality rate is very low or non-existent, while the healing time is significantly shortened [37].

A study conducted in Taiwan three years after a major explosion that injured 499 people aimed to investigate additional vitamin and mineral support for patients with severe burn injuries. There were significant differences between the group that received vitamin and mineral supplements compared to the control group in the incidence of wound infection, sepsis and days of hospitalization [44]. In addition to their antioxidant abilities, each of these compounds contributes to the wound healing process in a unique way. Thus, these compounds have the potential to provide physiological relief to patients suffering from thermal injury by balancing dysregulated oxidative stress and restoring cellular homeostasis. Therefore, natural antioxidants can reduce the harmful effects of various pathological conditions caused by oxidative stress [45, 46]. The practice of using raw natural plant products to treat multiple diseases has been going on for thousands of years without or with knowledge of their active antioxidant molecules long before the development of modern medicine with synthetic drugs and antioxidants [47, 48]. Today, it appears that they contribute to the normal development of the healing process, avoiding the deterioration of granulation tissue and acting in all phases of the wound healing process [49, 50]. They are safe to use and do not cause side effects [48].

Conclusion

The involvement of oxidative stress in the pathogenesis of thermally injured patients and its negative impact on the prognosis of burned patients is clear. The application of antioxidant therapy has shown significant benefits in improving the outcome of burns by shortening the healing time of wounds, reducing the incidence of infection, lowering the number of days of hospitalization and decreasing the mortality rate. However, more information is needed from the clinical trials on the use of antioxidant -rich natural products, especially in combination with other therapies.



Graph 1 The influence of antioxidants on mortality and healing time of burn wounds [37]

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