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Letters to the Editor / Cartas al Editor

THE NEUROSURGICAL WOUND: SLEEP AND FACTORS THAT CAN AFFECT THE HEALING MECHANISM

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Dear editor:

Wound healing is a complicated mechanism that aims to repair and heal injuries, however, if there is an inadequate process, it can lead to complications. These complications have an impact on the daily life of the individual, such as higher hospital costs, further procedures, and psychological impact[1].

Various factors influence healing, which can slow it down, and therefore increase morbidity and mortality and even poor cosmetic appearance in the individual. On the other hand, sometimes the wounds, and psychological sequelae that patients present can be undervalued and generate high costs[2]. Among the factors are the intrinsic ones, alluding to the state of health and others such as age, states of immunosuppression, and stress. On the contrary, extrinsic factors refer to situations such as malnutrition, infections, hypoperfusion, cancer, and radiation[3].

Immune activity may be influenced by sleep limitation, especially in the short term, and is related to the sympathetic system and the hypothalamic-pituitary-adrenal axis. This leads to a decrease in Natural Killer cells and an increase in circulating proinflammatory interleukins, increasing the risk of infection, pathologies, and impaired healing[4].

This document provides an overview of some factors that influence wound healing such as nutrition, oxygenation, stress, and, mainly, sleep. Mechanisms that are involved in these alterations are discussed.

FACTORS THAT OPTIMIZE WOUND HEALING

Pathological entities, intentional and accidental injuries to the skin, organic tissue, or mucosal surface, result in loss of tissue integrity leading to wound formation,[2]. Healing contains different sequential but overlapping phases, these are the hemostasis/inflammation phase, proliferation phase, and remodeling phase[23]. Once there is a tissue injury, platelet aggregation will be activated by the action of the exposed endothelium, collagen, and tissue factor, leading to degranulation, chemotaxis, and release of growth factors to form the clot and obtain correct hemostasis[5].

Different factors can intervene; intrinsic ones are referring to the individual's health status and if they have any predisposing elements or extrinsic ones such as malnutrition and infections[3].

Nutrition: Good nutrition plays an important role when it comes to tissue repair. It helps to create an environment to heal wounds that promote cell differentiation. For this reason, optimal amounts of nutrients and proteins are necessary to synthesize nucleic acids (DNA and RNA), proteins, and different elements involved in all these cellular processes[6]. Essential nutrients such as vitamin A promote healing because they participate in the epidermal growth factor, fatty acids, and omega-3 modulate the arachidonic acid pathway and carbohydrates in collagen formation[2].

Oxygenation: Adequate oxygenation is necessary to carry out correct healing, individuals under circumstances where the oxygen supply is not sufficient, lack optimal healing[2]. Oxygen is crucial in the process of inflammation, bactericidal action, angiogenesis, epithelial germination, and collagen deposition. Any interruption of oxygen supply such as cold, stress, or vasoconstriction by catecholamines or hypovolemia, can delay healing[3].

STRESS AND WOUND HEALING

Stress is a condition in which environmental loads cannot be tolerated by the individual, causing negative repercussions on behavior, affectivity, and other physiological processes, being part of the etiology of multiple pathologies[7]. There is a negative link between stress and healing, this is associated with an alteration in healing and an inadequate regulation of cells and molecules involved in the said process[8].

The hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary axes can be activated by stress, leading to the upsurge of glucocorticoids and catecholamines, which influence the healing process, especially in the initial inflammatory phase[1].

In older adults, a decrease in the number of macrophages has been observed, therefore, the secretion of proinflammatory cytokines and growth factors is reduced, preventing the correct recruitment and activation of leukocytes, stimulation of fibroblasts and keratinocytes, and promotion of angiogenesis in the wound. This process slowdown the inflammatory and proliferative phases[9].

Many studies show the relationship between emotional and psychological stress with increased mortality and morbidity[24-26]. The inflammatory markers are frequently researched aspects of the impact of stress, however, more research is required on micro-changes of the immune system in pathological results[8].

IMPLICATIONS IN CHRONIC AND POORLY HEALING WOUNDS

Wound healing requires oxygen to interact with numerous cytokines, serve as a supply to actively proliferating cells, and provide an effector for the respiratory burst of neutrophils[10-12]. It is estimated that a wound needs at least a tissue oxygen tension of 20 mmHg to heal properly, and oxygen tensions as low as 5 mmHg have been measured in non-healing wounds[1].

When other pathological factors come into play, such as an underlying disease state that can range from diabetes to cancer to malnutrition, a chronic wound can form[10,13,14]. The mechanism to reach this state can vary but includes factors that influence blood supply, alterations in immune function, metabolic diseases, medications, or local tissue damage[10]. External factors, such as sustained pressure, temperature, and humidity, also play an important role in allowing a wound to heal[10,15].

A sleep disorder characterized by instability of the upper airways during sleep, obstructive sleep apnea (OSA)[10,13,14,16], consisting of repetitive episodes of partial or complete narrowing or closure of the airways higher during sleep while respiratory effort continues, causes intermittent desaturation during sleep, sleep interruptions, and excessive daytime sleepiness[10,14,16]. In parallel, intermittent hypoxia and subsequent reoxygenation can lead to hypoxia/reperfusion injury with subsequent increased oxidative stress and production of vascular growth factors that can further impair wound healing[14]. In vitro, intermittent hypoxemia frequency and magnitude cycling markedly altered wound healing responses. The cell response can be very complex with obstructive sleep apnea desaturations[15].

OSA has a high prevalence in people with diabetes but is significantly underdiagnosed[13]. In patients with diabetes and OSA, intermittent hypoxia increases sympathetic activation and thus oxidative stress, impaired microvascular function, and inflammation, which could contribute to worse outcomes from diabetic foot ulcers, one of the most common complications. of diabetes, associated with a high risk of lower limb amputation and increased mortality[13,14,16]. In a recently reported case series of three people with diabetic foot ulcers, it was hypothesized that severe undiagnosed or untreated OSA contributed to the failure of ulcer healing, and they reported improved healing after starting treatment of OSA in 2 patients, while the third declined treatment with continuous positive airway pressure and reported much slower healing despite receiving full care of both the wound and its comorbidities[13]. Infection, ischemia, and inadequate pressure offloading are the three classic risk factors for nonhealing, and results to date suggest that OSA is potentially another modifiable risk factor for improved healing[14]. Future intervention studies should focus on examining the impact of OSA treatment on the development and progression of chronic and poorly healing wounds[13,14].

SLEEP AND TISSUE REGENERATION

The immune response differs between day and night[17]. The circadian rhythm, the coordination of the functions of the human body with the external cycles of light and darkness, is related to critical bodily changes such as hormone production, brain activity, heart, respiratory rates, body temperature, and tissue regeneration[18-20]. Cell division and protein synthesis reach their highest levels during sleep hours and decrease throughout the day, so the rate of healing of damaged tissues is higher during sleep[11,19]. Sleep is considered a restorative period in which the nervous system slows down its activity, leading to a state of partial unconsciousness[18-20]. A single sleep cycle is made up of 2

main phases, the non-rapid eye movement (non-REM) and rapid eye movement (REM) phases[19].

The first two stages of non-REM sleep involve changes in muscle and eye movement, respiratory rate, and body temperature[19]. These changes are followed by another two stages in which the decrease in brain delta waves results in deep sleep[17,19]. Growth hormone (GH), which is secreted after the delta stage of sleep, is responsible for growth in infancy and is crucial for ongoing tissue restoration and repair of damage incurred during waking hours[18,19,21].

Sleep disruption and neurosurgical wound healing are something not regularly brought up or discussed[27]. Prolonged duration of periodic desaturation can impact the wound healing process after neurosurgical procedures. Due to swings in intrathoracic pressure and obesity in combination with reduced central venous outflow, the wound healing can be slow and the risk of cerebrospinal leak can be present[22]. This is complicated with periodic desaturation. Further work is required to understand the interactions of these factors.

CONCLUSIONS

Lack of sleep is one of the crucial factors among factors, both intrinsic and extrinsic, known to influence the wound healing process. However, entities associated with sleep disturbances are generally underdiagnosed and adequate sleep is often not considered an integral part of therapy for wound management and healing. In addition, continuous positive airway pressure can improve the healing of diabetic foot ulcers, but given the lack of studies on the subject, randomized controlled intervention studies with a significant sample are required to verify and subsequently consider their inclusion in the chronic wound management guidelines.

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