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Review Article

The Potency of Asiatic Acid in Reducing Fibrosis after Strabismus Surgery *via* Type-2 Immunity Pathway: Review

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Abstract

Strabismus affects functionally, such as reducing binocular vision and causing diplopia, and also affects psychologically. Surgery is required for most strabismus cases, but excessive fibrosis can cause recurrent strabismus. Type 2 immunity is involved in the wound healing, and excessive inflammation from type 2 immunity can lead to excessive fibrosis. An extract from *Centella asiatica*, asiatic acid, has been studied that it can reduce inflammation and fibrosis in several organs. Asiatic acid can reduce inflammation caused by type 2 immunity by reducing IL-4. Asiatic acid has the potential to reduce fibrosis after strabismus surgery.

Keywords: Asiatic acid; *Centella asiatica*; Strabismus surgery; Type 2 immunity; Wound healing

Introduction

Strabismus is a condition in which both eyes cannot position the fovea towards an object viewed simultaneously, sometimes or all the time. Each eye's extraocular muscles and nervous system act as a sensorimotor unit whose function is to keep the eyeball in a straight position. The extraocular muscles, as a motor component, play a role in moving the 2 eyeballs so that the object being viewed can be focused on the fovea to form single binocular vision. The nervous system, as a sensory component, makes it possible to see the surrounding environment with depth perception (3 dimensions). These two components work simultaneously so that if there is a defect in just one component, it will cause strabismus [1].

Strabismus will cause one eye to fixate on an object while the fellow eye will fixate on another area. This results in each fovea receiving 2 different images, creating confusion in cortical perception. In children up to the age of 6 years-7 years, a suppression mechanism can arise caused by the cortex ignoring the weaker image, namely the image that falls on the peripheral part of the retina. Adults do not have a suppression mechanism, so two images received will give the perception that one object is in two different places; this condition is called diplopia or double vision, which is disturbing [2].

Management of strabismus aims to restore binocular vision function. Most cases of strabismus require surgical treatment. Strabismus surgery itself is a reconstructive procedure, not a cosmetic one because this surgical procedure has functional and psychological benefits for the patient. Apart from causing a decrease in binocular vision, strabismus also reduces the quality of life. Research from Estes et al. (2020) states that 27% of strabismus sufferers receive counseling regarding their mental health, and children with strabismus have a 3 times higher incidence of mental illness than adults. Strabismus surgery, from a psychosocial perspective, helps the patient's appearance meet society's normative expectations. Strabismus surgery helps cure the patient's social anxiety by making the patient's appearance more "normal" according to societal standards. This condition is the reason why strabismus needs to be treated [3-5].

Wound Healing

The wound healing process begins after strabismus surgery. The phases of wound healing include hemostasis, inflammation, proliferation, and remodeling. The hemostasis phase is the first phase of wound healing, and the goal is to stop bleeding due to vascular damage. The second phase of wound healing is the inflammatory phase, characterized by signs of inflammation such as edema and erythema in the wound. This phase aims to create immune protection against microorganisms that invade the wound by involving the humoral and cellular inflammatory systems. This phase is divided into early and late inflammatory phases. After coagulation, the initial inflammatory phase occurs with activation of the complement cascade and

neutrophil infiltration from 24 hours-36 hours after injury to prevent infection. Neutrophil cells carry out phagocytosis to destroy bacteria, foreign particles, and damaged tissue. This role is vital because the wound will not heal if bacteria are imbalanced. Cells that are damaged and experiencing necrosis will release Damage-associated Molecular Patterns (DAMPs), which will be recognized by Pattern Recognition Receptors (PRRs) from neutrophils, activating the immune response. Neutrophil activity will change within a few days after all contaminating bacteria have been eliminated, after which the neutrophils must be eliminated from the wound before proceeding to the next phase by apoptosis or extrusion onto the wound surface in the form of slough [6-12].

The late inflammatory phase occurs 48 hours–72 hours after injury. In this phase, macrophage cells are in the wound and continue phagocytosis. These cells originate from monocytes, which undergo phenotypic changes when they travel to the wound site. Macrophages have a longer lifespan than neutrophils and can work at low pH conditions. Macrophages are essential in this phase because they function as regulatory cells and providers of potent tissue growth factors such as Transforming Growth Factor-β (TGF-β), keratinocytes, fibroblasts, and endothelial cells. Lack of monocytes and macrophages in wounds will result in impaired wound healing due to poor wound debridement, inhibited proliferation and maturation of fibroblasts, and inhibited angiogenesis, resulting in inadequate fibrosis and weak wound healing. Lymphocytes are the last cells to arrive at the wound site in the late inflammatory phase, 72 hours after injury [6-8].

The proliferative phase begins on the third day after injury and lasts 2 weeks. This phase aims to close the wound, including angiogenesis, fibroplasia, and re-epithelialization. This phase is characterized by the migration of fibroblasts and the deposition of a new extracellular matrix of fibrin and fibronectin. On macroscopic examination, this process can be seen by the large amount of granulation tissue in the wound. The first process that occurs in the proliferative phase is fibroblast migration. Fibroblasts appear on the third day after injury due to TGF-β and PDGF produced by inflammatory cells and platelets. After arriving at the wound, fibroblasts will proliferate a lot and produce the matrix protein hyaluronan, fibronectin, proteoglycans, and procollagen types 1 and 3. The wound healing process requires collagen as an essential component. Collagen is made by activated fibroblasts and functions for tissue integrity and strength, especially in the proliferative and remodeling phases of the wound healing process. Collagen is the foundation of intracellular matrix formation. Extracellular matrix accumulation already forms in the first week. Activated fibroblasts will turn into myofibroblasts, have thick actin under the plasma membrane, and produce pseudopodia that attach to fibronectin and collagen in the extracellular matrix. These cells then retract, and wound contraction occurs. Wound contraction is important to help the wound healing process by approximating the ends of the wound. The condensed extracellular matrix will form a space filled with new collagen. The collagen accumulation in the wound area will form avascular and acellular scar tissue, with 80%-90% of type 1 collagen and the rest of type 3 [6,7,11].

The remodeling phase is the final phase of the wound healing process and aims to form new epithelial and scar tissue. The formation of the extracellular matrix begins with the formation of granulation tissue. This phase can last for 1 year to 2 years or even longer. The remodeling process in acute wounds requires a regulatory mechanism to maintain the balance between synthesis and degradation so that wound healing occurs normally. In the maturation of the intracellular matrix, the diameter of the collagen bundles increases, and hyaluronic acid and fibronectin are degraded. The tensile strength of the wound increases progressively with the addition of collagen. Collagen fibers can gain up to 80% of their original strength compared to healthy tissue [6,7].

Collagen synthesis, breakdown, and extracellular matrix remodeling continue to occur for 3 weeks after injury. Matrix metalloproteinase enzyme is responsible for collagen degradation. This enzyme is produced by neutrophils, macrophages, and fibroblasts. Tissue inhibitor regulates the action of matrix metalloproteinase. As time goes by, the activity of this inhibitor increases so that the action of matrix metalloproteinase decreases and triggers the accumulation of the new matrix. The composition of collagen, which was initially irregular, becomes more and more regular in the final phase of remodeling. Connective tissue shrinks in size and brings the edges of the wound closer to each other due to the interaction of fibroblasts and extracellular matrix, after which the density of fibroblasts and macrophages will decrease by apoptosis. Capillary growth will stop, blood flow to the wound area will decrease, and metabolic activity in the wound area will decrease. The final result of the wound healing process is entirely mature scar tissue with a reduced number of cells and blood vessels and high tensile strength [6,7].

Type 2 immunity role in wound healing

Tissue damage after strabismus surgery will give rise to type 2 immunity in that tissue, where type 2 immunity involves IL-4, IL-5, IL-13, and recruitment of eosinophils. Damaged cells will release DAMPs, recognized by PRRs from neutrophils, activating the innate immune response by signaling IkB Kinase (IKK) to Phosphorylate Nuclear Factor-kB (NF-κB). NF-κB is also produced from the Phosphatidylinositol 3-Kinase (PI3K) signaling cascade and is inhibited by Nuclear Factor Erythroid 2-Related Factor (Nrf2). In the adaptive immune response, NF-κB will activate B cells and T cells so that these 2 cells will differentiate and proliferate, where T cells can differentiate into T Helper 1 (Th1), Th2, Th9, and Th17. Th2 will produce IL-4, IL-5, and IL-13 and stimulate mast cells, basophils, and eosinophils [13-15].

Eosinophils, as part of type 2 immunity from acute muscle tissue damage, play an important role in muscle regeneration.

Eosinophils produce type 2 cytokines, namely IL-4 and IL-13. These cytokines play a role in differentiating T cells into Th2, which produces IL-4, IL-5, and IL-13 again. The response from IL-4 and IL-13 will cause fibroblast cells to produce collagen, which helps close the wound. This pathway is also called the type 2 fibrosis pathway. Apart from that, IL-4 will stimulate cells in striated muscle, namely Fibrogenic/Adipogenic Progenitors (FAPs), to produce IL-33 and proliferate, which will then differentiate into fibroblast cells. IL-33 will stimulate group 2 Innate Lymphoid Cells (ILC2s) to produce IL-4, IL-5, and IL-13. IL-5 will recruit eosinophils. In chronic and highly polarized type 2 immune response conditions, eosinophils become excessive. Excessive eosinophils in this condition can cause fibrosis due to persistent and excessive signaling, causing excess extracellular matrix deposition, which causes scarring and fibrosis [13,16-18].

Excessive Fibrosis after Strabismus Surgery

Fibrosis is a natural process to restore tissue function for healthy wound healing. Excessive wound healing is a form of aberrant wound healing, often involving excessive fibroblast function and excessive accumulation of extracellular matrix during the wound healing process. Excessive wound healing will cause detrimental scar tissue to form and the tissue to become dysfunctional. Such scar tissue arises due to increased and prolonged inflammation, so the wound healing process becomes suboptimal [10,19].

Excessive scarring that occurs after strabismus surgery can cause recurrent strabismus through several mechanisms, depending on what tissue is affected. If it occurs in muscles, fibrosis will result in the shortening of the muscles, resulting in excessive muscle action. In adhesions syndrome, fibrosis occurs in various layers of tissue around the muscles; this causes the movement of the eyeball to become restricted. Fibrosis of the pulley will result in changes in muscle function. Fibrosis of the conjunctiva will cause the position of the eyeball to shift, and there will be a restriction to the movement of the eyeball in the opposite direction from the area of fibrosis. Resurgery in cases like this aims to restore the position of the eyeball and optimize eyeball movement; however, in cases of heavy scar tissue formation, the operation's aim may only be to position the eyeball centrally. A report from Repka et al. stated that the incidence of resurgery in strabismus patients in the United States reached 6.72% [20,21].

Discussion

Asiatic acid role in wound healing

Centella asiatica is a plant from the Apiaceae family and is widespread in Southeast Asia, such as Indonesia and Malaysia. This plant is also known as Gotu Kola. *Centella asiatica* contains large amounts of pentacyclic triterpenoid saponins, including asiatic acid, asiaticoside, brahmic, brahmoside, brahminoside, centelloside, madecassoside, sceffoleoside, and thankuniside. Asiatic acid ($C_{30}H_{48}O_5$) is the most prominent component of *Centella asiatica*, and this compound has various effects from studies, including but not limited to being anti-oxidant, anti-tumor, anti-inflammatory, and enhancing wound healing [22-25].

Asiatic acid has a role in the wound healing process. Somboonwong et al. (2012) conducted research using *Centella asiatica*, which was extracted using various methods and found that the asiatic acid component in *Centella asiatica* extract was the most potent component that played a role in the wound closure process. In another study conducted by Bian et al. (2013) using keloid tissue cultures containing keloid fibroblasts and normal fibroblasts, it was shown that asiatic acid plays a role in preventing keloids by reducing TGF-β-induced collagen type 1 in keloid fibroblasts. The role of asiatic acid in healing wounds on the eye was studied by Kurniasih et al. (2021); they studied the administration of subconjunctival asiatic acid at a dose of 0.4 mg/0.5 mL after trabeculectomy surgery. The result was that subconjunctival asiatic acid at a 0.4 mg/0.5 mL dose after trabeculectomy surgery could reduce fibroblasts [26-28].

Another role of asiatic acid is as an anti-inflammatory. Inflammation itself is the initial phase of wound healing. Asiatic acid inhibits pro-inflammatory cytokines by reducing activation of NF-κB *via* the IKK pathway and upregulating Nrf2, which inhibits NF-κB. Inhibition of NF-κB theoretically also causes inhibition of IL-4 expression. Moon, et al. (2021) researched the administration of asiatic acid in cases of atopic dermatitis in mice. In this study, it was found that IL-4 expression decreased with the administration of asiatic acid. Chen et al. (2017) used asiatic acid in human corneal epithelial cell cultures that were inflamed using lipopolysaccharide; the inflammatory factors studied were decreased. The liver organ was also inflamed by lipopolysaccharide in the research of Xu et al. (2017); the liver experienced a decrease in inflammation after administering asiatic acid, which has the benefit in case of inflammation due to post-ischemia reperfusion. Research by Yang et al. (2018) showed that asiatic acid reduced inflammation caused by cisplatin, which can cause acute kidney disorders [6,13,15,22,29-33].

Conclusion

A balanced wound healing is needed to ensure the optimal outcome of strabismus surgery. Type 2 immunity has a role in wound healing, but excessive inflammation can cause excessive fibrosis, which can cause recurrent strabismus. Asiatic acid has an anti-inflammatory and anti-fibrotic effect, based on several studies. Further research is needed to prove the efficacy of asiatic acid in reducing inflammation and fibrosis after strabismus surgery.

Conflict of Interest

The authors declare that they have no conflict of interest.

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