EFFECT OF LASER THERAPY ON INFLAMMATION IN PNEUMONIA OR PNEUMONIA SEPSIS THROUGH THE NF-KB REGULATORY PATHWAY: A LITERATURE REVIEW STUDY

Rahmad[1,2], Irawati Djaharuddin[1], Yanuar Rahmat Fauzi[2], Bethasiwi Purbasari[2], Annisatul Hakimah[2], Yose Waluyo[1]

[1]Faculty of Medicine, Hasanuddin University, Makassar
[2]Faculty of Medicine, Brawijaya University, Malang

eISSN: 2828-4070
Proceedings ICE on IMERI. 2024.
Received: November 29th, 2024
Accepted: January 2nd, 2025
Published online: January 17th , 2025

Corresponding Author
Name : Rahmad
Email : rahmadanwar1983@ub.ac.id

Abstract

Pneumonia is the most frequent cause of death from infectious diseases is the eighth leading cause of death in the United States. Meanwhile, sepsis and septic shock remain the leading causes of death among critical patients despite decades of significant advances in supportive therapy. A major factor leading to high morbidity and mortality from septic shock is the lack of effective treatment. Many different options have been proposed, among which the prospect of low-level laser therapy is being discussed quite actively. Laser therapy is a viable way to treat pneumonia or sepsis pneumonia. It is known for its benefits as an anti-inflammatory effect that can reduce the levels of pro-inflammatory cytokines, namely IL-6, as well as increase TNFα levels and enhance the balance of inflammatory processes. Additional research is required to confirm the effect of laser therapy on inflammation, especially the NF-kB pathway in cases of pneumonia or sepsis pneumonia in vitro, in vivo and in clinical studies.

Keywords

Pneumonia sepsis, laser therapy, inflammation

Introduction

Pneumonia and other lower respiratory tract infections are the third leading cause of death globally. In developed nations like the United States, pneumonia is the most common fatal infectious disease, with an incidence of 12 cases per 1,000 people and a mortality rate of 15%.[1] Epidemiological data suggest that the median age of pneumonia

patients ranges from 49 to 57 years. The hallmark clinical symptoms of this disease include high fever, muscle aches, dry cough, and shortness of breath.[2]

Pneumonia is a syndrome associated with sepsis and septic shock, encompassing various pathological processes, including systemic inflammation.[3] The disease is typically classified into two main categories: community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP), with the latter including ventilation-associated pneumonia (VAP).[4]

Pneumonia is a major contributor to severe sepsis and the primary cause of mortality.[5] Sepsis and septic shock remain the primary drivers of death among critical patients despite years of effort and substantial progress in supportive care. A key factor contributing to the high rates of morbidity and mortality from septic shock is the absence of an effective treatment.[3]

Several options have been suggested, and low-level laser therapy (LLLT) is an actively discussed approach. The anti-inflammatory effects of LLLT and low-intensity light irradiation (LILI) have been extensively and thoroughly researched; LILI is likely the most widely utilized application of low-level laser therapy today.[6] Given this background, this article aims to determine the effect of laser therapy on inflammation in sepsis pneumonia through the NF-kB regulatory pathway, as a literature review study.

Method

This study was a literature review which collected articles from Pubmed, Science direct, and Google scholar published from 2006 until 2023. Twenty two studies were collected but only 16 articles were discussed.

Results

Study shows that the transcription factor NF-κB, which induces the expression of inflammatory mediators, plays an important role in preventing the occurrence of pneumonia. During sepsis, a signaling pathway leads to the activation of NF-κB. The effect of bacterial toxins on NF-κB activity is dramatic and extensive, leading to a significant increase in NF-κB activity across all the studied organs, which is consistent with the involvement of diverse organs in septic shock. The researchers report that the cellular

mechanism of PBM is regulated by the Toll-4 receptor (TLR4) signaling pathway and ROS activation, ultimately inducing the NF-KB factor and increasing the levels of pro-inflammatory cytokines such as IL-6, IL-1β, and IL-8.

Discussion

Pneumonia is the outcome of a multifaceted process in which infectious microorganisms penetrate the lower respiratory system. This respiratory infection can be contracted in the community or a hospital setting, and spread through the aspiration or inhalation of pathogenic microorganisms. Understanding the role of these disease-causing microbes in the underlying cause of pneumonia is crucial for providing the patient with appropriate clinical care and treatment.[1]

The inflammatory process in pneumonia occurs when pathogens invade the body, and the inflammatory response is a protective mechanism employed by the body. If the pathogen is not eliminated, the inflammatory response will persist and lead to tissue damage. While a sufficient inflammatory response is required to clear the bacteria, excessive inflammation can result in ongoing local or systemic harm.[1]

The pathogenesis of pneumonia is closely linked to how certain microbial variations interact with the host's inflammatory response. In the United States, the most prevalent bacterial cause of community-acquired pneumonia (CAP) in both children and adults is *Streptococcus pneumoniae*. This pathogen has been observed to exhibit significant variations in its ability to activate the NF-κB pathway within macrophages. NF-κB is a crucial transcription factor responsible for the induction of various pro-inflammatory cytokines.[7]

Mizgerd et al. demonstrated that many inflammation-related genes are essential for defending against pneumonia. The transcription factor NF-κB, which induces the expression of inflammatory mediators, plays an important role in preventing the occurrence of pneumonia. During sepsis, a signaling pathway leads to the activation of NF-κB. Septic shock is a clinical syndrome with diverse underlying causes, and NF-κB is activated by various pro-inflammatory cytokines and bacteria released during sepsis, making it the ultimate target of such septic shock triggers. The kinetics of NF-κB activity induced by different bacterial pathogens vary, with β-glucan from the pathogenic fungus

Pneumocystis carinii causing a much slower and longer-lasting induction of NF-κB activity compared to lipopolysaccharide (LPS). Early-phase NF-κB activation is mediated by LPS and other inflammatory mediators, while late-phase activation is driven by TNF-α and IL-1β. The effect of bacterial toxins on NF-κB activity is dramatic and extensive, leading to a significant increase in NF-κB activity across all the studied organs, which is consistent with the involvement of diverse organs in septic shock.[7]

Several different options have been proposed, including the prospect of LLLT, also known as *Photobiomodulation* therapy (PBMT), which is being actively discussed. The anti-inflammatory effects of LLLT and LILI have been thoroughly researched; this property of laser light is likely the most widely utilized aspect of low-level laser therapy today.[6] Recent studies have shown promising results of PBM in reducing acute lung inflammation. Consequently, the use of PBM can be an effective therapy for managing respiratory or inflammatory diseases such as pneumonia. PBM therapy has been identified as a non-invasive treatment for inflammatory conditions.[8] The use of supplemental LLLT or PBMT has been recommended as a potential treatment modality to reduce cytokine storms, Acute Respiratory Distress Syndrome (ARDS), and ventilator needs in COVID-19.[9]

PBMT using LLLT and light-emitting diodes (LEDs) are non-thermal therapies that utilize coherent and incoherent light beams, respectively. Both LLLT and LED therapies produce similar effects through the absorption of photons by chromophores in tissue-specific wavelengths. These non-invasive therapies irradiate tissues to activate cellular photoreceptors. Lasers are absorbed by internal photoreceptors such as cytochrome c oxidase, porphyrin, and light-sensitive ion channels, while photons from LEDs are absorbed by light-sensitive ion channels, leading to an increase in intracellular calcium ions (Ca^{2+}). Cytochrome c oxidase, which is part of the mitochondrial respiratory chain, absorbs red and near-infrared wavelengths, resulting in increased electron transport, mitochondrial membrane potential, and adenosine triphosphate (ATP) production. This process activates several signaling pathways involving cyclic adenosine monophosphate, nitric oxide (NO), Ca^{2+}, and reactive oxygen species, followed by the activation of transcription factors such as hypoxia-inducible factor 1-alpha (HIF-1α), nuclear factor erythroid 2-related factor 2 (NRF2), and nuclear factor-κB (NF-κB), leading to a substantial genetic response directed at inflammation, proliferation, and repair. Based on this

mechanism, PBM is an effective treatment that promotes tissue repair and regeneration, pain relief, wound healing, reduction of oxidants, and anti-inflammatory effects.[10]

In cases of acute lung inflammation, LLLT can increase tumor necrosis factor-alpha (TNFα) levels and help restore the balance of inflammatory processes. It significantly reduces the levels of interleukin-8 (IL-8), can alleviate acute respiratory distress syndrome (ARDS), and lowers mortality rates.[11] Photomodulation therapy also contributes to healing by promoting the apoptosis (programmed cell death) of inflammatory cells while suppressing apoptotic pathways in lung tissue. In models of acute lung injury, low-intensity laser therapy reduced DNA fragmentation and apoptotic pathway activity by increasing the levels of B-cell lymphoma-2 (Bcl-2) cells, a key regulator of the intrinsic or mitochondrial pathways for apoptosis in alveolar epithelial cells, while promoting DNA fragmentation in inflammatory cells.[12]

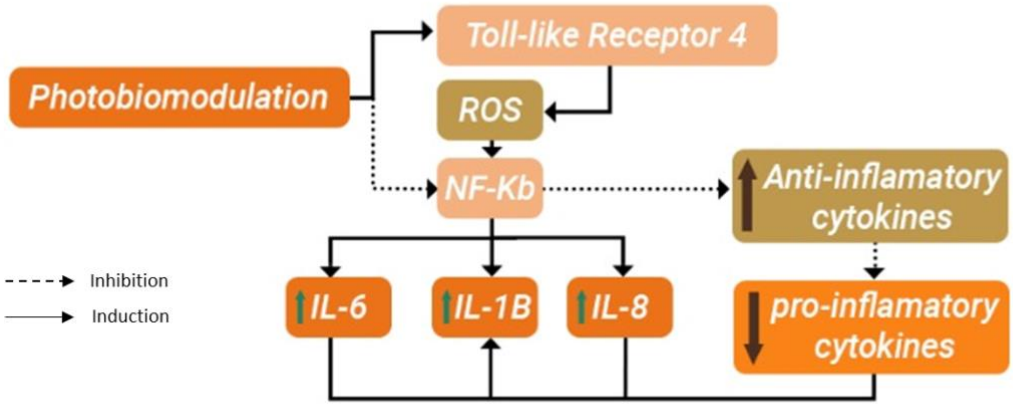

Figure 1. Mechanism of NF-kB Inflammatory Pathway Induced by Photobiomodulation.

Experimental studies have demonstrated that LLLT can modulate the excessive inflammatory response known as a cytokine storm, as well as acute respiratory distress syndrome (ARDS), through its anti-inflammatory properties. Animal models of acute airway and lung inflammation show that LLLT can reduce the leakage of pulmonary microvessels, lower levels of inflammatory cytokines like IL-1β and IL-6, and decrease intracellular reactive oxygen species. LLLT appears to reduce inflammation through multiple mechanisms, suggesting it may be an effective strategy for controlling cytokine storms.[9]

In another study, it was demonstrated that LLLT at a dose of 7.5 J/cm2 and a wavelength of 660 nm was able to alleviate airway inflammation induced by LPS through

a mechanism involving the reduction of the pro-inflammatory cytokine interleukin-1 beta (IL-1β). This is a significant effect of LLLT because it is well-established that IL-1β plays an important role in the inflammatory process.[13]

Conclusion

Pneumonia accompanied by excessive inflammatory conditions can cause local or systemic damage that occurs continuously, triggering post-infection sepsis. We discussed in detail the inflammatory mechanism mediated by the NF-kB pathway against pneumonia and the pathophysiology of sepsis. LLLT is a viable way to treat sepsis pneumonia. It is known for its benefits as an anti-inflammatory able to reduce levels of pro-inflammatory cytokines, namely IL-6, as well as increase TNFα levels and improve the balance of inflammatory processes. Further studies are needed to confirm the effect of laser therapy on inflammation, especially the NF-kB pathway in cases of pneumonia or sepsis pneumonia in vitro, in vivo, and clinical studies.

Competing Interests

The authors declare that there is no conflict of interest in this article.

References

1. Ferreira-Coimbra J, Sarda C, Rello J. Burden of community-acquired pneumonia and unmet clinical needs. Adv Ther. 2020 Apr;37(4):1302–18.
2. Nejatifard M, Asefi S, Jamali R, Hamblin MR, Fekrazad R. Probable positive effects of the photobiomodulation as an adjunctive treatment in COVID-19: A systematic review. Cytokine. 2021 Jan;137:155312.
3. Liu SF, Malik AB. NF-κB activation as a pathological mechanism of septic shock and inflammation. American Journal of Physiology-Lung Cellular and Molecular Physiology. 2006 Apr;290(4):L622–45.
4. Torres A, Cilloniz C, Niederman MS, Menéndez R, Chalmers JD, Wunderink RG, et al. Pneumonia. Nat Rev Dis Primers. 2021 Apr 8;7(1):25.
5. Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M. Corticosteroids for pneumonia. Cochrane Database Syst Rev. 2017 Dec 13;12(12):CD007720.

6. Moskvin S, Askhadulin E, Kochetkov A. Low-level laser therapy in prevention of the development of endothelial dysfunction and clinical experience of treatment and rehabilitation of COVID-19 patients. Giallauria F, editor. Rehabilitation Research and Practice. 2021 Jan 26;2021:1–8.
7. Mizgerd JP. Inflammation and pneumonia. Clinics in Chest Medicine. 2018 Dec;39(4):669–76.
8. Azadeh SS, Esmaeeli Djavid G, Nobari S, Keshmiri Neghab H, Rezvan M. Light-based therapy: Novel approach to treat COVID-19. Tanaffos. 2023 Mar;22(3):279–89.
9. Sigman S, Mokmeli S, Vetrici M. Adjunct low level laser therapy (LLLT) in a morbidly obese patient with severe COVID-19 pneumonia: A case report. Can J Respir Ther. 2020 Sep 28;56:52–6.
10. Lu YS, Chen YJ, Lee CL, Kuo FY, Tseng YH, Chen CH. Effects of photobiomodulation as an adjunctive treatment in chronic obstructive pulmonary disease: a narrative review. Lasers Med Sci. 2023 Jan 28;38(1):56.
11. Carvalho JL, Britto A, De Oliveira APL, Castro-Faria-Neto H, Albertini R, Anatriello E, et al. Beneficial effect of low-level laser therapy in acute lung injury after i-I/R is dependent on the secretion of IL-10 and independent of the TLR/MyD88 signaling. Lasers Med Sci. 2017 Feb;32(2):305–15.
12. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, et al. Reduction and functional exhaustion of T cells in patients with Coronavirus Disease 2019 (COVID-19). Front Immunol. 2020 May 1;11:827.
13. Aimbire F, Ligeiro De Oliveira AP, Albertini R, Corrêa JC, Ladeira De Campos CB, Lyon JP, et al. Low level laser therapy (LLLT) decreases pulmonary microvascular leakage, neutrophil influx and IL-1β levels in airway and lung from rat subjected to LPS-induced inflammation. Inflammation. 2008 Jun;31(3):189.