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The Role of Acupuncture in Regulating Inflammatory Cytokines in Sepsis

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Abstract: *Sepsis has been known since 2000 years ago and until now is one of the oldest and hardest problems in medical practice. Along with advances in knowledge about the pathogenesis of sepsis, there are many developments in diagnosis and therapy. Acupuncture is one of the modalities of medical therapy that can regulate the immune system, with minimal side effects. The purpose of this review is to gather evidence that acupuncture may hold promise for treating inflammatory diseases such as sepsis. From various studies indicates that acupuncture can regulate inflammatory mediators, to reduce TNF- α, IL-1, IL-6 and increse anti-inflamamtory mediator IL-10 Through these mechanisms, acupuncture is expected to play a role in the treatment of sepsis.*

Keyword: *acupuncture, inflammatory, sepsis*

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I. Introduction

Until now sepsis is one of the oldest and most difficult problems in the practice of medicine. Along with the advancement of knowledge about the pathogenesis of sepsis, there are many developments in diagnosis and therapy. Some consensus on sepsis that has been agreed and applied internationally has made it easier for doctors in the management of sepsis . However, the incidence of sepsis, severe sepsis, and sepsis shock continues to increase. Several studies show that there is a change in the etiological pattern of sepsis, formerly mostly caused by Gram negative bacteria, and is currently mostly caused by Gram positive bacteria. At the same time, sepsis due to yeast infection also showed a drastic increase.[1] Sepsis can cause a very significant burden in the public health system. In worldwide, 13 million people have sepsis every year and as many as 4 million people die.[2] Insidens sepsis is expected to increase by 1.5% annually. In Europe there is an incidence rate of 37% in sepsis. Factors of age and sex affect the mortality rate in sepsis. Mortality rates are higher in the elderly population> 85 years than children. Mortality rates in women are lower.[3]

Inflammatory factors play a significant role in the pathophysiology of sepsis. Where there is a release and activation of excessive inflammatory mediators. These inflammatory mediators include both local and systemic cytokines, neutrophil activation, monocytes, macrophages, endothelial cells, platelets, and cells other, activation of plasma protein cascade such as complement, coagulation system and fibrinolysis.[4, 5] Recent studies show the benefits of acupuncture in sepsis through anti-inflammatory mechanisms. Acupuncture is a safe therapeutic modality with minimal side-effects, proven to reduce inflammatory mediators such as TNF-α, IL-1, and IL-6 and increase anti-inflammatory mediator IL-10.[6-12] As expected acupuncture may play a role in sepsis management.

II. Pathogenesis of Sepsis

Sepsis is also called the malignant intravascular inflammatory process. A complex and potent immunological cascade becomes the primary protective response to the invasion of microorganisms in humans. The presence of deficiencies in the body's defense system allows for infection, but if there is an excessive response it can harm the host through maladaptive release of inflammatory compounds produced.[13] The nonspecific immune system comprises the cellular immune system (polymorphonuclear leukocytes, macrophages, natural killer cells, and dendritic cells) and humoral immune systems, the first line of body defense against invading pathogens. The role is to limit bacterial growth and replication, and most importantly is to exclude pathogenic microorganisms. The role of this nonspecific immune system is localized at the site of infection. If an excessive immune response develops and a systemic response to infection results in sepsis.[2, 4, 14]

Inflammatory mediators are a host defense mechanism against infection and invasion of microorganisms. Host immunity reacts by releasing endogenous proteins and activation of immune cells so that microorganisms can be killed, damaged cells are cleansed, and tissue repair develops. In sepsis there is release

and activation of excessive inflammatory mediators. These inflammatory mediators include both local and systemic cytokines, neutrophil activation, monocytes, macrophages, endothelial cells, platelets, and the activation of plasma protein cascades such as complement, coagulation and fibrinolysis systems. is released into its own autocrin process and releases other inflammatory mediators including interleukin-1 (IL-1), platelet activating factor, IL-2, IL-6, IL-8, INF and nitric oxide, further raising the levels of cytokines. This leads to the activation of PMN leukocytes, macrophages, and lymphocytes. Furthermore, proinflammatory medications recruit more of these cells (paracrine process). All of these processes will lead to destructive immunological conditions. Sepsis is an autodestructive process that causes an extension of the normal pathophysiological response to infections involving other normal tissues.[13,15] TNF-α, IL-1β and IL-6 are the most actively released pro-inflammatory mediators. These cytokines will increase the adhesion of leukocyte endothelial cells, inducing the release of both proteases and arachidonic acid metabolites, and activating the coagulation cascade. Interleukin-6 appears to be a major mediator of coagulation activation. Subsequent release of arachidonic acid metabolites such as A2 thromboxane, prostacycline, and prostaglandin E2 for many common clinical signs and symptoms associated with SIRS, including fever, tachycardia, tachypnea, ventilation-perfusion abnormalities, and lactic acidosis.[13]

Simultaneously, anti-inflammatory cytokines such as IL-10 become negative feedback mechanisms for inflammatory reactions. This anti-inflammatory cytokine mediates the anti-inflammatory compensatory response syndrome (CARS) through inhibition of TNF-α, IL-6, T-lymphocytes, and macrophage function. If there is an imbalance between SIRS and CARS, homeostasis is not achieved and various clinical sequelae may occur. If the SIRS is dominant, it can be septic shock and / or disseminated intravascular coagulation (DIC). If CARS is dominant, the immune system is suppressed, causing the patient to be susceptible to life-threatening infections. Ultimately, major organ hypoperfusion may occur (ie, kidney, mesenterium, brain, liver), the end result being a multiple organ dysfunction syndrome.[16,17]

Intravascular thrombosis, an important component of the local inflammatory response, helps prevent invading microorganisms and prevents infection and inflammation from spreading to other tissues. Another important aspect in the pathogenesis of sepsis is a change in the balance of procoagulants - anticoagulants. Increased procoagulant factors and decreased anticoagulant factor. LPS will stimulate more endothelial cells to express tissue factor (TF) that will activate coagulation. If TF is expressed on the cell surface, it binds to a factor VIIa forming an active complex that can activate the X and IX factors. Then the fibrinogen will be converted to fibrin, causing the formation of microvascular thrombus and further damage.[4, 18] Anticoagulant factors (protein C, protein S, antithrombin III, and tissue factor-pathway inhibitor / TFPI) will modulate the coagulation process. The α-thrombin is bound to thrombomodulin to activate protein C by binding to endothelial protein C receptors. Activated C proteins will activate Va and VIIIa factors and inhibit the synthesis of plasminogen-activator inhibitor-1 (PAI-1). Activated C proteins will also decrease apoptosis, leukocyte adhesion, and cytokine production. Sepsis will lower levels of protein C, antithrombin III, and TFPI. Lipopolysaccharides and TNF-α will also decrease the synthesis of TFPI, activated protein C (APC) and antithrombin (AT) which will interfere in the inhibition of fibrin formation. There is also an increase in the synthesis of PAI-1 which will inhibit fibrinolysis.[18,19] While IL-6 activates TF, it affects the activation of thrombin to form fibrin.[19]

III. Mechanism of Acupuncture

Acupuncture is one of the stress induces that can stimulate the Hypothalamic pituitary adrenal axis (HPA). Through the HPA axis, humoral substances are secreted and channeled to target organs through the blood vessels. Stress with certain levels triggers the hypothalamus secrete Corticothropin Releasing Hormone (CRH) which further stimulates the anterior pituitary gland to release Adenocorticothropin hormone (ACTH). ACTH stimulates the adrenal glands to release glucocorticoids that regulate immune function.[20]

Acupuncture has been used as a therapy in various inflammatory diseases including sepsis. EA at ST36 point has anti-inflammatory effect. Based on EA research it can induce anti-inflammation by reducing inflammatory cytokines TNF-α, IL-6, IL-1β and increase IL-10. The involvement of the vagus nerves in the mechanism of acupuncture as an anti-inflammatory action is crucial. Previous research has indicated that the stimulation of the vagus nerve can specifically regulate the production of inflammatory cytokines through a cholinergic pathway, which relies heavily on the functional integrity and anatomy of the vagus nerve. This is evidenced by vagotomy in animals trying to eliminate the effects of acupuncture as anti-inflammatory.[9] Stimulation of the vagus nerve will cause the release of acetylcholine which will bind to its receptor in macrophages which will inhibit the cytokines TNF-α, IL-1.[20] In addition Torres-Rosas et al reported that EA in ST36 may increase myoelectric gastric activity in mice and this effect depends on the vagus nerve. Electroacupuncture can regulate systemic inflammation through DOPA decarboxylase activation which will lead to increased dopamine in the adrenal medulla. Dopamine inhibits cytokine production through dopaminergic receptors of type 1.[10] Zhu et al and Guang et al report that ST36 acupuncture point stabulation may increase CD3 +, CD4 +, CD8 +, CD4 + / CD8 + in sepsis in both experimental and human animals.[11,21]

Lan et al undertook a study to analyze suppression of the TLR4 / NF-κB inflammatory pathway by using electroacupuncture. This research was conducted on mouse experimental animals using acupuncture point LI11 Quchi and ST36 Zusanli. The results of this study concluded that electroacupuncture can suppress the activation of TLR4 / NF-κB along with inflammatory mediators such as TNFα, IL-1β and IL-6.[22] Meanwhile, Wang et al conducted a study in rats to analyze electroacupuncture effects on TLR2 / 4 in adrenalectomy-induced mice. From these studies it was concluded that electroacupuncture in addition to inhibiting TLR2 / 4 mRNA expression may also inhibit TNFα, IL-1β and IL-6 mRNA expression.[23] Yim, et al investigated the effect of ST36 Zusanli electroacupuncture on anti-inflammatory drugs in arthritis-induced mice. The study found decreased levels of IL-6, INF-γ, TNFα cytokines in the EA group.[24] Lee, et al conducted a study to analyze the effect of EA on the regulation of cyclooxygenase formation. The experiments were conducted on mouse-fed animals by injecting carrageenan substances in the animal's claws to induce inflammation. Performed stabbing on acupuncture points ST36 Zusanli and SP6 Sanyinjiao with EA frequency used is 2 Hz, 15 Hz and 120 Hz. From the research results can be concluded that EA 2 Hz inhibits the formation of COX-1 and COX-2.[25]

Based on the latest acupuncture research, acupuncture can also affect Peroxisome Proliferator Activated Receptors (PPAR) that play a role in inflammation. Giving acupuncture or electroacupuncture can stimulate PPAR activation thus inhibiting transcription of proinflammatory cytokine cytokines.[26, 27] PPAR has a key role as a regulator of energy homeostasis and inflammation. PPAR γ activation may inhibit the inflammatory response factor expression and activity gene in human monocytes / macrophages by repressing *nuclear factor kappa B* (NF-κB). PPAR γ activation also has anti-inflammatory effect. The anti-inflammatory properties of synthetic PPARγ agonists can also be described, in part, with the ability to inhibit the production of TNF-α and other proinflammatory cytokines (Figure 1). PPAR bonds with coactivators reduce the level of available coactivators to bind to pro-inflammatory transcription factors such as NF-κB thus decreasing the transcription of a number of pro-inflammatory genes, including various interleukins.[28-30]

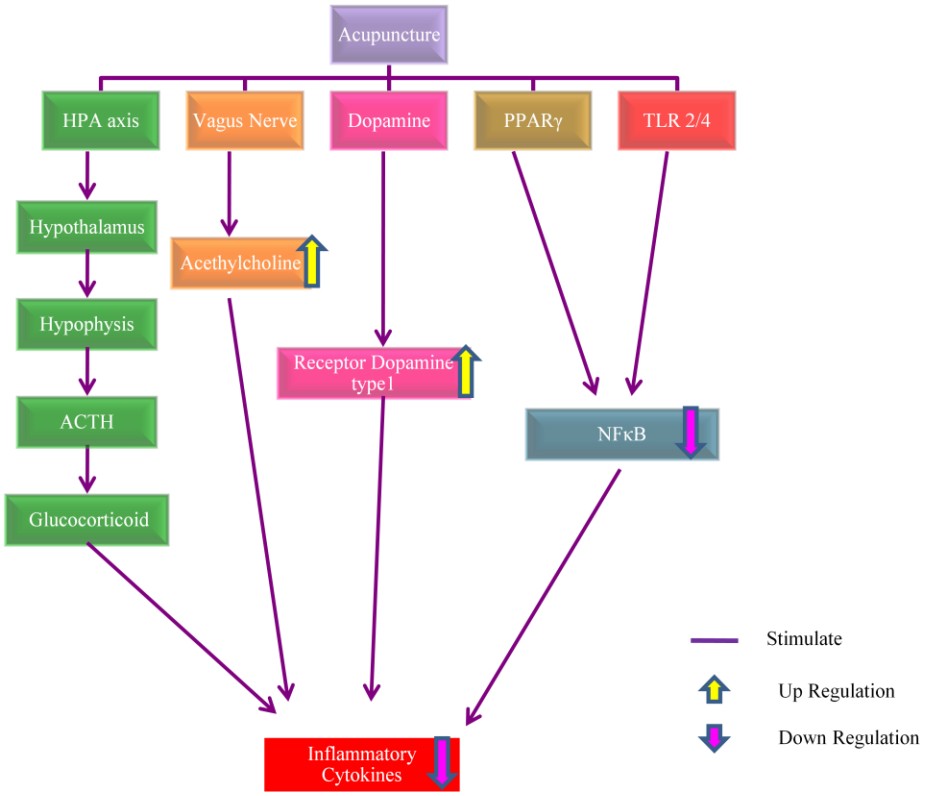

Figure 1. The mechanism of acupuncture in regulating inflammatory cytokines

IV. Research on Acupuncture

Szabo et al conducted a study on mice to assess the effectiveness of acupuncture in sepsis. Assessment is done by counting the number of neutrophils and bacteria in the rat peritoneum. Induction of sepsis in mice is done by ligation and stabbing on the caecum so that it will cause bacteria to enter the peritoneal cavity and cause sepsis. Acupuncture treatment is divided into 2 protocols. Each of the protocols contained 4 treatment groups:

control group without sepsis induction, non lethal sepsis group, grouplethal sepsis, lethal sepsis group with acupuncture. In the first protocol the acupuncture points used were ST36 and GV1. Manual acupuncture stimulation was performed at 0, 2 and 4 hours after sepsis induction. In the second protocol the acupuncture points used are BL25, GV1, GV3, GV14, LR2, LI11, Ex-HN6. Manual acupuncture stimulation was performed at 0, 1.5, 4.5, 6, 10, 14 hours after sepsis induction. The results showed that the first protocol could increase the number of neutrophils and decrease the number of bacterial colonies in the peritoneum compared with the second protocol. From these studies it can be concluded that acupuncture has a role in sepsis.[6]
eady been defined by NCEP 2013 report.

Bechara et al conducted a study to assess the effects of acupuncture therapy on the concentrations of TNF-α, IL-1β and IL-10 in peritonitis mice. There were three treatment groups in the study: control group, sham acupuncture group and acupuncture group with 4 rats in each group. Induction of peritonitis is performed by injecting carrageenan substance intraperitoneally. Manual acupuncture stimulation was performed at 10 minutes and 2 hours after induction of peritonitis. The acupuncture points used are GV1, GV20, Ex-HN3. In the sham group the acupuncture point used is 1 cm laterally from the acupuncture point that has been used. The results showed that there was a significant decrease in IL-1β concentrations in the acupuncture group compared with the control group. From the study it was concluded that acupuncture therapy could inhibit the production of IL-1β.[7]

Wang et al conducted a study to assess the effectiveness of electroacupuncture in septic patients. Research subjects taken from ICU divided into 2 groups each there are 34 people. The control group received standard sepsis therapy such as anti-infective, anti-shock, respiratory support, and nutritional support therapy. While in treatment group got combination therapy that is acupuncture and standard therapy sepsis. Indicators assessed were C-reaction protein (CRP), IL-6, TNF-α, APACHE II score, HLA-DR CD14 +, duration of ICU care, duration of ventilator use and death on day 28. Measurements taken before and after therapy. Acupuncture points used were ST36, BL10, ST37, ST39 for 3 consecutive days with frequency 2 times a day. Electroacupture therapy given frequency of 4 Hz with continuous wave for 60 minutes. The results showed that in the treatment group the concentrations of CRP, IL-6 and TNF-α were significantly lower than the control group. HLA-DR CD14 + measurements were significantly higher in the treatment group than in the control group. APACHE II scores after therapy were significantly lower than before therapy in the treatment group.[8]

Bastida et al conducted a study to assess the effect of electroacupuncture on sepsis using a mouse animal model. Sepsis induction was performed with rat caecal ligation puncture (CLP). In the study there were 4 treatment groups ie CLP group, CLP group, CLP group with sham acupuncture and CLP group with acupuncture. The acupuncture point used was ST36 with 30 Hz electroacupuncture frequency for 20 min. Indicators assessed were TNF, IL-6, HMGB1. In the study performed vagotomy and inhibition of catecholamines by using drugs. The results showed that electroacupuncture can decrease inflammatory factors in sepsis.[9]

Torres et al conducted a study on mice with sepsis with lipopolysaccharide induction. Sepsis induction is done by CLP method. Acupuncture point used in the research is ST36 Zusanli using electrical stimulation with frequency 10 Hz for 15 minutes. Indicators assessed in the study were TNF, IL-6, Interferon-γ (IFN-γ), monocyte chemotactic protein-1 (MCP-1). In addition to the examination of inflammatory mediators in the study conducted various experiments to determine the mechanism of acupuncture as an anti-inflammatory such as peroneal and tibial neurectomy, sciatic neuroctomy, adrenalectomy, vagus nerve stimulation, dopamine expression. From these studies it can be concluded that electroacupuncture can suppress inflammation in sepsis through sciatic nerve stimulation, vagus and induce dopamine expression.[10]

Zhu et al conducted a study on mice with sepsis with CLP induction. There were 5 treatment groups with each number of rats subjects as much as 20 individuals ie 1) sham group with laparotomy, 2) CLP-induced sepsis group, 3) low frequency EA group with CLP, 4) high frequency EA group with CLP, 5) group EA preconditioning (5 electroacupuncture was performed once a day prior to CLP). Acupuncture point used is ST36 Zusanli for 30 minutes with a frequency of 2 Hz and 100 Hz. Indicators assessed in the study were percentages of CD3 +, CD4 +, CD8 +, T lymphocytes. From the results of this study can be concluded that electroacupuncture on ST36 Zusanli can significantly increase the percentage of CD3 +, CD4 +, CD8 +, T lymphocytes.[11]

Silva et al conducted research on rats undergoing peritonitis to determine the anti-inflammatory effect of acupuncture manual. Induction of peritonitis is performed by injecting carrageenan substances as much as 0.5 ml to intraperitoneal. There were two major groups in the study. In the first group the rats were divided into 4 small groups ie the control group with saline injection, carrageenan group without treatment, the DEXA carrageenan group and the SP6 carrageenan group. The parameters measured in the group were TNF-α, IL-1β and IL-10, infiltration inflammatory cells, vascular permeability. From the group it was concluded that SP6 point stabbing could significantly increase IL-10, suppress vascular permeability and inflammatory cell infiltration. In the second group of mice received the main treatment of adrenalectomized and sham

adrenalectomized. Each group will be subdivided into 4 small groups ie saline control group, carrageenan group, DEXA carrageenan group and SP6 carrageenan group. Parameters measured in the group were infiltration of inflammatory cells and vascular permeability. From the group it was concluded that SP6 points could not suppress inflammatory cell infiltration and vascular permeability in adrenalectomized groups. From these studies it can be concluded that the SP6 acupuncture points depend on the adrenal glands and increase IL-10 as an anti-inflammatory.[12]

Guang et al conducted a study to evaluate the effects of electroacupuncture on septic patients. There were 60 patients divided into 2 groups: the control group received routine sepsis treatment and the treatment group received electro-acupuncture with routine sepsis treatment. The acupuncture points used are ST36 Zusanli and CV4 Guanyuan points. Parameters used in the study were mortality on day 28, measurement of Acute Physiology and Chronic Health Evaluation score (APACHE) -II, CD3 +, CD4 +, CD8 +, CD4 + / CD8 +, monocyte of human leukocyte antigen (HLA). From the study, 5 patients died in the treatment group (17.2%) and 9 patients died in the control group (31%). There was an increase in CD3 +, CD4 +, CD8 +, CD4 + / CD8 +, HLA in the treatment group versus the control group. APACHE-II measurements decreased significantly in the treatment group versus the control group. From the research it can be concluded that electroacupuncture at point ST36 and CV4 can increase curative effect in sepsis patients.[21]

Song et al conducted a study to assess the effects of electroacupuncture on rats undergoing sepsis induced by lipopolysaccharide (LPS). The acupuncture points used in the study were LI4 Hegu and PC6 Neiguan with frequency of 2/100 Hz dense disperse. Mice received electroacupuncture intervention 45 minutes before induction and 2, 4, 6 hours after sepsis induction The measured parameters were survival rate, inflammatory cytokine TNF-α, IL-6, IL-1β, IL-10 antiinflammatory cytokine. From the research it was found that electroacupuncture at point LI4 and PC6 can increase survival rate, and decrease inflammatory cytokine.[31]

V. Discussion

Inflammation is a highly regulated body's defense process. Loss of control in this system can cause a number of diseases including rheumatoid arthritis, neurodegenerative disorders, inflammatory bowel diseases, and sepsis. Fueled by various physical, chemical, biological, inflammatory agents is the cumulative result of genetic susceptibility factors and various responses. Although the inflammatory response differs in each disease, it can be characterized by a common spectrum of endogenous gene and mediator involved, including growth factor, inflammatory cytokines such as IL-1β, TNF-α and IL-6.[32]

In sepsis there is release and activation of excessive inflammatory mediators. This inflammatory mediator includes both locally and systemically working cytokines; activation of neutrophils, monocytes, macrophages, endothelial cells, platelets, and other cells; activation of plasma protein cascade such as complement, coagulation system and fibrinolysis. In addition to proinflammatory mediators, antiinflammatory mediators such as IL-10 anti-inflammatory cytokines are also released.[4] Various cytokines contribute to the inflammatory process, most importantly tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, IL-8, IL-12 as proinflammatory cytokines and IL-10 , IL-1 receptor antagonist (IL-1ra) as an anti-inflammatory cytokine.[4, 5] Another important aspect in the pathogenesis of sepsis is a change in the anticoagulant- procoagulant balance. Increased procoagulant factors and decreased anticoagulant factor. Lipopolysaccharides and TNF-α will decrease the synthesis of TFPI, activated protein C (APC) and antithrombin (AT) which will interfere in the inhibition of fibrin formation. While IL-6 will activate TF which will affect the activation of thrombin to form fibrin.[19] By forming fibrin systemically will interfere with perfusion to various tissues. So it can cause organ dysfunction.

Acupuncture which is one of the stress induces can stimulate the HPA axis. Various humoral substances are secreted and channeled to target organs through blood vessels through HPA axis. Acupuncture stimulation will trigger hypothalamus secrete CRH which will then stimulate the anterior pituitary pelvic to release ACTH. ACTH will stimulate the adrenal glands to release glucocorticoids. Given the glucocorticoids in sepsis cases it regulates the immune function.[20] Various studies have been done in the management of sepsis by using acupuncture. EA droplets at ST36 point have anti-inflammatory effect with reduction of inflammatory cytokines. The involvement of the vagus nerves in the mechanism of acupuncture as an anti-inflammatory action is crucial. Studies in mice show that electrical stimulation of the vagus nerve can directly protect the septic state of shock. Stimulation will trigger a number of signaling complexes that will inhibit the formation of inflammatory cytokines of TNF-α, IL-6, IL-1β. Although this therapy is very promising but its application requires surgical procedures in the vagus nerve and difficult to apply to critical patients.[9] The formation of inflammatory cytokines is closely related to the pro-inflammatory transcription factor NF-κB. Various acupuncture studies have been conducted by focusing on NF-κB to control inflammation. Acupuncture can affect NF-κB through inhibition of cell signaling TLR and activate PPARγ. [26, 27] Based on existing studies, it is expected that acupuncture can be helpful in the management of sepsis.

VI. Conclusion

Research acupuncture on management sepsis has been done and given good result. Acupuncture has deep benefits management of sepsis is by lowering the inflammatory mediator so it can help the condition in sepsis patients. Acupuncture can be considered as an adjunctive therapy in patients with sepsis. However, further research is needed to achieve optimal results.

References

[1]. Martin GS. Sepsis, severe sepsis and septic shock: changes in incidence, pathogens and outcomes. Expert Rev Anti Infect Ther. 2012 Jun;10(6):701-6.
[2]. Levy MM. Introduction. In : Daniels R, Nutbeam T, eds. ABC of sepsis. Singapore : Wiley-Blackwell. 2010:1-4.
[3]. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J. Pinsky MR. Epidemiology of severe sepsis in the United States : analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001
[4]. Chen K, Widodo D. Patofisiologi sepsis : peran mediator inflamasi. Dalam : Widodo D, Pohan HT, eds. Bunga rampai penyakit infeksi. Jakarta. Pusat Penerbitan Departemen Ilmu Penyakit Dalam FKUI. 2004:54-62.
[5]. Ventetuolo CE, Levy MM. Sepsis : a clinical update. Clin J Am Soc Nephrol 2008;3:571-577.
[6]. Szabo MVR, Bechara GH, Ferreira SH, Cunha FQ. Effect of various acupuncture treatment protocols upon sepsis in wistar rats. Ann NY Acad Sci.2004; 1026:251-256.
[7]. Szabo MVR, Bechara GH, Ferreira SH, Cunha FQ. Effect of acupuncture on TNF-α, IL-1β and IL-10 concentration in the peritoneal exudates of carrageenan-induced peritonitis in rats. Ciencia Rural. 2005; 35(1):103-108.
[8]. Wang LC, Wu JN. The clinical efficacy of sepsis with early intervention of electroacupuncture. Life Science Jounal. 2013; 10(3): 1900-03.
[9]. Bastida AV, Rosas RT, Pizano L, Estrada J, Acosta A, Eutimio M. Electrical stimulation at the ST36 acupoint protect against sepsis lethality and reduces serum TNF levels through vagus nerve and catecholamine-dependent mechanisms. Evidence-Based Complementary and Alternative Medicine. 2014: 1-8.
[10]. Rosas RT, Yehia G, Pena G, Mishra G, Bonilla M, Eutimo M, et al. Dopamine mediates the vagal modulation of the immune system by electroacupuncture. Nat Med.2014;20(3):291-295.
[11]. Zhu MF, Xing X, Lei S, Wu JN, Wang LC, Huang L, Jiang R. Electroacupuncture at bilateral zusanli points (ST36) protects intestinal mucosal immune barrier in sepsis. Evidence-Based Complementary and Alternative Medicine. 2015 : 1-7.
[12]. Da Silva MG, Guginski G, Werner M, Baggio CH, Marcon R, Santos A. Involvement of interleukin -10 in the anti-inflammatory effect of sanyinjiao (SP6) acupuncture in a mouse model of peritonitis. Evidence-Based Complementary and Alternative Medicine. 2011 : 1-9.
[13]. Khafaji AH, Sarma S, Eschun G. Multi organ dysfunction syndrome in sepsis. Upadated May 16, 2016. Diunduh dari www.medscape.com pada 1 September 2016.
[14]. Kendrick SFW, Jones DEJ. Mechanisms of innate immunity in sepsis. In : Baudoiun S. Sepsis. London. Springer. 2008:5-10.
[15]. Monsel A, Zhu Y, Gennai S, Hao Q, Liu J, Lee J. Cell-based therapy for acute organ injury preclinical evidence and ongoing clinical trials using mesenchymal stem cells. Anesthesiology. 2014; 121: 1099-121.
[16]. Kanji S, Devlin JW, Piekos KA, Racin E. Recombinant human activated protein c, drotrecogin alfa (activated): A novel therapy for severe sepsis. Pharmacotherapy. 2001; 21(11): 1389-1402.
[17]. Riedemann NC, Guo RF, Ward PA. Novel strategies for the treatment of sepsis. Nature Medicine. 2003; 9(5): 517-523.
[18]. Russell JA. Management of sepsis. N Engl J Med 2006;355:1699-1713.
[19]. Choi G, Schultz M, Levi M, Poll T. The relationship between inflammation and the coagulation system. Swiss Med Wkly. 2006; 136: 139-144.
[20]. Kavoussi B, Ross E. The neuroimmune basis of anti-inflammatory acupuncture. Integrative Cancer Therapies. 2007; 6(3): 251-257.
[21]. Guang Y, Rui-ying H, Ai-jing D, Yu H, Li J.Effects of electro-acupuncture at zusanli, guanyuan for sepsis patients and its mechanism through immune regulation.Chin J Integr Med. 2016; 3: 219-224.
[22]. Lan L, Tao J, Chen A, Xie G, Huang J, Lin J, et al. Electroacupuncture exerts anti-inflammatory effects in cerebral ischemia-reperfusion injured rats via suppression of the TLR/NF-κB pathway. Int J Mol Med 2013;31:75–80.
[23]. Wang J, Zhao H, Mao-Ying QL, Cao XD, Wang YQ, Wu GC. Electroacupuncture downregulates TLR2/4 and pro-inflammatory cytokine expression after surgical trauma stress without adrenal glands involvement. Brain Res Bull 2009;80:89–94.
[24]. Yim YK, Lee H, Hong KE, Kim Y, Lee BR, Son C,et al. Electro-acupuncture at acupoint ST36 reduces inflammation and regulates immune activity in collagen-induced arthritic mice. Evid Based Complement Alternat Med .2007;4:51–7.
[25]. Lee JH, Jang KJ, Lee YT, Choi YH, Choi BT. Electroacupuncture inhibits inflammatory edema and hyperalgesia through regulation of cyclooxygenase synthesis in both peripheral and central nociceptive sites. Am J Chin Med.2006;34:981–988.
[26]. Zhang Y Tang CL, Tian Y, Yuan HZ, Yang H, Tang NZ, Gao RQ, Cao J. Effects of Electroacupunctrue Combined with Dietary Control on Peroxisome Proliferator-activa-ted Receptor-α, and Liver Fatty Acid-binding Protein Levels in Non-alcoholic Fatty Liver Disease Rats. Zhen Ci Yan Jiu.2015; 40(5).
[27]. Jing X Ou C, Chen H, Wang T, Bin Xu, Lu S, Zhu BM. Electroacupuncture Reduces Weight Gain Induced by Rosiglitazone through PPAR. Evidence-Based Complementary and Alternative Medicine. 2016; 2016:12.
[28]. Ahmadian M, Suh JM, Hah N, Liddle C, Atkins A, Downes M, et al. PPARγ signaling and metabolism: the good, the bad and the future. Nature Medicine. 2013; 19(5): 557-563.
[29]. Wahli W, Michalik L. PPARs at the crossroads of lipid signaling and inflammation. Trends in endocrinology and metabolism.2012; 23(7): 351-363.
[30]. Knethe A, Soller M, Brune B. Peroxisome proliferator-activated receptor γ (PPARγ) and sepsis.Arch Immunol Ther Exp. 2007;55 : 19-25.
[31]. Song JG, Li H, Cao Y, Xin Lv, Zhang P, Li Y, et al. Electroacupuncture improves survival in rats with lethal endotoxemia via the autonomic nervous system. Anesthesiology. 2012; 116: 406-14.
[32]. Kaminska B. MAPK signaling pathways as molecular targets for anti-inflammatory therapy-from molecular mechanisms to therapeutic benefits. Biochimica et Biophysica Acta. 2005; 1754: 253-262.

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