Vagal nerve stimulation: less explored entity in surgical patients

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Editor:- Perioperative systemic inflammatory response syndrome (SIRS) after laparotomy, thoracotomy, emergency surgeries leads to uncontrolled release of pro- inflammatory cytokines, tumor necrosis factor (TNF)-α, interleukin-1 (IL-1) and high mobility group box- 1(HMGB1). SIRS can progress to sepsis, septic, multi-organ failure and coagulopathy. This cascade is balanced by anti-inflammatory factors like cytokines IL-10, IL-4, soluble TNF receptors, IL-1receptor antagonists and transforming growth factor (TGF) β.[1] These counter-regulatory factors are not always sufficient to control the effects of inflammatory factors. Vagus nerve is known to modulate this response by decreasing release of pro-inflammatory cytokines from macrophages. This effect is mediated by cholinergic anti-inflammatory pathway (CAP) wherein there is an interaction of acetylcholine (ACh) with α7 subunit containing nicotinic – bungarotoxin – sensitive ACh receptors (α7nAChR) on macrophages and other immune cells.

CAP is a neural mechanism that regulates immunologically-mediated inflammation and tissue injury by suppression of pro-inflammatory cytokine expression. Vagal afferent sensory fibres transmit information to brain about the ongoing inflammatory process. Ach is an important neurotransmitter of vagus which attenuates release of pro-inflammatory cytokines-TNF-α, IL-1βand IL-6. Central and peripheral effect of Ach is mediated by muscarinic and nicotinic receptors. Both afferent and efferent components of vagus nerve are involved in co-ordinating the inflammatory cascade.

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On stimulation, efferent component increases Ach release which binds on α7n AChR of macrophages and immune cells which inhibits synthesis and release of pro-inflammatory cytokines.[2]

Vagal nerve stimulation has been shown to prevent deleterious effects of cytokines in experimental sepsis, endotoxemia, ischaemia/reperfusion injury (stroke), haemorrhagic shock, rheumatoid arthritis and other inflammatory syndromes. It has also been approved for treating refractory seizures and depression. Tracey et al described the role of CNS in orchestrating major physiological responses through innervated circuits like control of heart rate, blood pressure, temperature, digestive system, blood sugar levels.3This could be used to interfere with cytokines production pharmacologically or electrically.

Vagus nerve is considered an extension of CNS to visceral organs especially reticuloendothelial system (spleen and liver) which produces cytokines. Spleen mediates reduction in cytokines production due to vagal stimulation. Several researchers questioned the association of CAP and spleen. Vagal preganglionic neurons innervate coeliac ganglion from which postganglionic sympathetic neurons formed splenic nerves which justified the role of spleen in CAP.[4] It was also observed that vagal stimulation was not associated with reduced cytokine levels in post-splenectomy patients.

Vagus also coordinates manifestation of SIRS in the form of fever by transmitting information to brain via sensory fibres. Bernik et al stimulated intact vagus nerve in adult male Lewis rats pharmacologically and electrically after subjecting them to endotoxin-induced shock. They used CNI-1493 which is a tetravalent guanyl-hydrazone molecule that inhibits

systemic inflammation. They found that intracerebroventricular CNI-1493 was 100,000 times more effective than IV.[5]Animals who underwent surgical or chemical vagotomy had unresponsive shock despite treatment with CNI-1493 because a functional CAP is required for anti-inflammatory effect in vivo.

Electrical stimulation of either side intact vagus nerve also attenuated endotoxin induced SIRS. At present, CNI-1493 is not approved for use in humans. The only way of electrical vagal stimulation is via surgically placed catheters which is not feasible in sick surgical patients. Pavlov et al suggested vagus nerve non-invasively with acupuncture, meditation, hypnosis and biofeedback.

The anti-inflammatory properties of vagal nerve stimulation is mediated by its afferent fibres i.e. via activation of hypothalamico-pituitary-adrenal (HPA) axis and efferent fibres i.e. the CAP fibres. Further studies are required to establish the safety and efficacy of vagal nerve stimulation perioperatively. Once it is proven using large cohorts undergoing different types of surgical procedures, perioperative SIRS can be addressed and morbidity due to systemic inflammatory mediators can be reduced.

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