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REVIEW

The New Orientation of Postoperative Analgesia: Remote Ischemic Preconditioning

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Purpose of Review: Postoperative analgesia is currently a significant topic in anesthesiology. Currently, the predominant approach for achieving multimodal analgesia involves the utilization of pharmacotherapy and regional anesthesia procedures. The primary objectives of this approach are to mitigate postoperative pain, enhance patient satisfaction, and diminish overall opioid usage. Nevertheless, there is a scarcity of research on the use of remote ischemia preconditioning aimed at mitigating postoperative pain.

Recent Findings: Transient stoppage of blood flow to an organ has been found to elicit remote ischemia preconditioning (RIPC), which serves as a potent intrinsic mechanism for protecting numerous organs. In addition to its established role in protecting against reperfusion injury, RIPC has recently been identified as having potential benefits in the context of postoperative analgesia.

Summary: In addition to traditional perioperative analgesia, RIPC provides perioperative analgesia and organ protection.

Keywords: postoperative pain, remote ischemic preconditioning, inflammation, opioids

Introduction

One study reported that more than 50% of patients suffer from postoperative pain.[1] On average, 312.9 million people worldwide undergo surgery annually,[2] which means that hundreds of millions of patients suffer from suboptimal postoperative pain control.[3] Insufficient management of pain leads to heightened susceptibility to morbidity and the development of persistent postsurgical pain, as well as prolonged hospitalization and a greater burden on the patient's family. Traditionally, opioids have been the major drugs used for postoperative pain management. However, in recent years, the development of enhanced recovery after surgery (ERAS) protocols has introduced a multimodal analgesia method. This technique aims to target various pain receptors and pathways by utilizing a mix of different medications and administration routes. The goal is to produce enhanced analgesic benefits while minimizing the occurrence of adverse effects.[4,5] Remote ischemic preconditioning (RIPC) is a physiological mechanism and a particular protocol whereby brief ischemia in limbs protects distant tissue or organs from prolonged ischemia through either humoral mediators or neuronal pathways. Its noninvasive nature and promising experimental results have led to numerous clinical studies validating the organ-protective effects of RIPC. These important organs include the heart, lung, brain, liver and kidneys.[6–11] In addition, RIPC also plays a certain role in postoperative analgesia. Thus, we reviewed the application of RIPC for postoperative pain and explored the potential analgesic mechanism, aiming to provide a new direction for perioperative analgesia.

Clinical Application

Memtsoudis et al[12,13] first demonstrated that RIPC is related to reducing postoperative pain, and then, they conducted a further study on the influence of RIPC on postoperative pain. A total of sixty patients who were scheduled for unilateral total knee arthroplasty (TKA) with the use of a tourniquet were included in this study. Half of the patients were randomly assigned to undergo a limb preconditioning procedure involving inflation of the tourniquet for 5 min, followed by

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deflation and a subsequent reperfusion period of 5 min. The study revealed that individuals in the preconditioning cohort experienced considerably reduced postoperative pain levels, including during periods of rest and physical activity.

It remains to be studied whether the application of RIPC to nonsurgical sites can also reduce postoperative pain. In their study, Pereira et al[14] conducted experiments on patients who were undergoing normal cholecystectomy. The RIPC technique was employed by inflating a pneumatic tourniquet on the lower limb, namely, at the thigh, with a pressure of 100 mmHg above the systolic pressure for 5 min. The study revealed that compared with non-RIPC, RIPC could reduce morphine use in postoperative patients who underwent cholecystectomy.

These studies demonstrate that RIPC could help with postoperative pain control and may provide an organ-protective effect in addition to providing analgesia, which more strongly conforms to global trends in effective postoperative pain management guidelines.[15–17]

Analgesia Mechanism

Inflammation

Postoperative pain is the result of inflammation and injury to the nerve trunk or peripheral fibers.[18] There are distinct categories of inflammation, specifically, classic inflammation, neurogenic inflammation, and neuroinflammation, each of which has distinct functions in the experience of pain. Pain is elicited by the direct activation and sensitization of nociceptors through the action of inflammatory mediators.[19,20] A diverse range of inflammatory mediators, including bradykinin, prostaglandins (eg, PGE2), H+, ATP, nerve growth factor (NGF), and proinflammatory cytokines and chemokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and CCL2, have been identified.[19,21–23]

Konstantinov et al revealed that RIPC can decrease the expression of proinflammatory genes and increase the expression of anti-inflammatory genes. These genes are believed to be involved in various cellular processes, including leukocyte adhesion, chemotaxis, cell adherence/migration, apoptosis, the TNF-α signaling pathway, and the Toll-like receptor pathway.[24] An experimental mouse model was subjected to transient unilateral hindlimb ischemia, resulting in alterations in gene expression related to oxidative stress, inflammation, and mitochondrial function during both the early and later stages after the procedure.[25] The administration of RIPC prior to the prolonged application of a hindlimb tourniquet in rats resulted in notable outcomes, including a decrease in the inflammatory cell response, a reduction in the rate of apoptotic cell death, and an increase in the microcirculation.[26] A decrease in the expression of proinflammatory genes was observed. Conversely, there was an increase in the expression of genes associated with the mitigation of the oxidative stress response, whereas the expression of genes with the ability to exacerbate oxidative injury decreased. Specifically, the protection conferred by RIPC was evidenced by a decrease in neutrophil activity and contact between leukocytes and endothelial cells.[27,28]

The trials demonstrated a notable disparity in support of RIPC as it relates to the reduction in inflammatory marker levels, including those of interleukin (IL)-6, IL-1β, interferon γ, and tumor necrosis factor (TNF)-α.[10,29–32] RIPC can cause downregulation of the expression of proinflammatory genes, which results in reduced levels of inflammatory circulating cytokines.[33] Thus, the alleviation of postoperative pain by RIPC may be related to a decrease in inflammatory mediators.

Interleukin 6 (IL-6)

Li et al[10] randomly selected 216 patients who underwent thoracic pulmonary resection under one-lung ventilation with propofol–remifentanil anesthesia and were randomized 1:1 to receive either limb RIPC or conventional lung resection. Three cycles of 5-min ischemia/5-min reperfusion induced by a blood pressure cuff served as the RIPC stimulus. Compared with those in the control group, the serum levels of interleukin-6 and tumor necrosis factor-α in patients who underwent RIPC were significantly lower at 6, 12, 24, and 48 h after the operation. Moreover, the incidence of acute lung injury and the length of postoperative hospital stay were markedly reduced by limb RIPC compared with patients in the control group. However, among the 20 patients who underwent open cholecystectomy, the RIPC group experienced postoperative pain relief but no significant change in IL-6 levels.[14] Among the 60 patients who underwent TKA, there was also no significant difference in intra-articular IL-6 levels in those who received RIPC compared to controls.[13]

Even so, the degree of pain after TKA and nonlaparoscopic cholecystectomy was significantly reduced. The dose of postoperative analgesics administered in the former group was no significant change, while the dose of morphine in the latter group was significant reduction. The reason may be related to the choice of anesthesia method. In the former, intraspinal anesthesia combined with nerve block was used, while in the latter, only intraspinal anesthesia was used. Since regional anesthesia may affect the perioperative inflammatory response, the effect of RIPC may have been underestimated in this case. Due to the difference in the pain score between 6 h and 12 h after surgery was large, the use of nerve blocks covers the analgesic effect of RIPC, resulting in a certain degree of difference in the use of postoperative analgesic drugs. Compared with general anesthesia, intraspinal anesthesia can better control postoperative pain, so further studies on the effect of RIPC without the influence of regional anesthesia techniques are needed.

Tumor Necrosis Factor α (TNF-α)

TNF-α is the main inflammatory mediator involved in the mechanism of RIPC. He et al[32] selected 90 elderly patients over 65 years of age who underwent colon surgery, 45 of whom were given RIPC. Compared with that in the control group, the serum TNF-α concentration in RIPC patients was lower on the first and third days after surgery but not on the seventh day. Similarly, a study revealed significantly lower serum TNF-α concentrations on the first and second days after surgery in 108 patients who underwent pulmonary resection with RIPC than in controls.[10] However, the opposite result was also found. In 30 patients who underwent TKA surgery, RIPC was applied, and there was no significant difference in TNF-α levels after surgery.[13]

Interleukin 1β (IL-1β)

We detected decreased levels of IL-6 and IL-1β in a limb ischemia test in pigs compared to animals who did not receive ischemia treatment, and decreased levels of IL-1β were also detected in elderly RIPC patients who underwent colon surgery compared to control patients.[32]

Neuropeptides

The activation and subsequent release of neuropeptides, including substance P, CGRP, and prostanoids, are primarily mediated by nociceptors, particularly C-fibers. The activation of nociceptors leads to the occurrence of neurogenic inflammation, a significant factor contributing to the experience of pain associated with complex regional pain syndrome (CRPS).[34] The application of RIPC has been shown to have a significant impact on patients with early complex regional pain syndrome (CRPS). This effect is attributed to the anti-inflammatory properties of RIPC, which serve to mitigate vascular disruptions and minimize blood shunting. Consequently, RIPC leads to a reduction in blood flow and an increase in oxygen extraction in affected individuals.[35]

Not all patients treated with RIPC showed a reduction in inflammatory marker levels, and there was no significant difference in inflammatory mediator levels in the RIPC group compared with the control group during TKA, shoulder surgery, living kidney transplant, or pancreatic surgery.[36–39] The reasons for the differences in the above results may be as follows. First, the differences may be related to the choice of anesthesia. Different anesthesia modes may have different effects on the inflammatory response of perioperative patients. The use of propofol under general anesthesia has an inhibitory effect on RIPC, while the use of lidocaine may mask the analgesic effect of RIPC.[40]

The type of surgery is one of the key factors affecting the release of inflammatory mediators. Most patients who undergo invasive or prolonged surgery may be in a state of relative ischemia. For example, the release of a tourniquet during TKA produces a severe inflammatory response, and reperfusion injury after ischemia is induced.[13,36] When RIPC was applied to mice with spinal cord ischemia–reperfusion injury, motor function was restored and improved, and RIPC had an important protective effect on nerves.[41] Surgical tissue injury triggers activation of both proinflammatory and anti-inflammatory pathways, and RIPC significantly reduces IL-6, IL-1β and TNF-α levels in lung resection and colon surgery, while no significant changes in inflammatory factor levels are observed in pancreatic and gallbladder surgery;[10,14,32,39] this may be related to the less extensive ischemia–reperfusion injury than that seen in lung and colon surgery.It may also be related to the small number of patients in these studies, and it is necessary for us to increase the research subjects and expand the scope of research to prove the inhibitory effect of RIPC on inflammatory mediators.

Differences in the preconditioning time and intensity of RIPC may also affect the release of inflammatory mediators, which may be the reason why IL-1β and TNF-α levels did not decrease on the 7th day after colon surgery.[32] Most studies have used three or four 5-min intervals of upper or lower limb ischemia interspersed with 5-min reperfusion periods; however, these are empirical choices, and the optimal RIPC mode has not yet been determined. Therefore, the expression of inflammatory mediators following RIPC varies depending on multiple factors(Table 1).

Opioids

Shimizu and colleagues conducted a series of experiments to examine the humoral characteristics of limb RIPC and its impact on isolated rabbit heart models.[42] The findings of the study indicated that the transfer of plasma and dialysate obtained from donor rabbits undergoing RIPC and using a dialysis membrane with a molecular weight cutoff of 15 kDa provided protection to animals that were not previously preconditioned. However, this protective effect was no longer observed in subjects who were pretreated with naloxone, suggesting the potential involvement of the opioid receptor pathway. The present results demonstrate that the RIPC effect is eliminated when the spinal cord is transected at the T9-T10 level and that the spinal opioid receptor is selectively blocked with naloxone methiodide.[43,44]

RIPC was applied to patients undergoing routine cholecystectomy, and visual analog scale scores at rest and during deep breathing and coughing were reduced, as was morphine use within 24 h after surgery.[14] Therefore, it is speculated that the analgesic effect of RIPC may be related to the release of endogenous opioids, which leads to a reduction in morphine consumption during the postoperative period. A recent study revealed that RIPC can modulate pain sensitivity by reducing the total time under pain;[45] however, absolute pain intensity was not affected. Endogenous opioids can effectively reduce pain intensity, but a certain intensity and duration of exercise are required to achieve an analgesic effect, so it is necessary to enhance RIPC stimulation to reduce pain intensity.

Multiple extracellular signaling molecules, including adenosine, bradykinin, and opioids, have been recognized as mediators and effectors, providing support for the notion that opioids play a role in contributing to RIPC.[46] The modulation of ascending pain can occur through the release of opioids and the activation of opioid receptors at the peripheral, spinal, or supraspinal level.[47] RIPC has been found to enhance the functionality of potassium-ATP channels.[48] Cell hyperpolarization leads to a decrease in excitability and a decrease in pain signals because potassium-ATP channels are activated. The analgesic mechanism of action of opioids involves the opening of potassium channels in postsynaptic neurons; based on this we found that the release of endogenous opioids through RIPC may serve as a mechanism for pain modulation, and the synergistic effect of the two can reduce the degree of pain in RIPC patients and reduce the consumption of morphine.

Table 1 Expression of Inflammatory Mediators in RIPC

Operation Type	Number of Patient	Anesthesia Method	Ripc Setting	Inflammatory Mediators
TKA[13]	60	Intravertebral anesthesia +nerve block anesthesia	Lower extremity 250mmHg	IL-6(-), TNF-α(-)
TKA[36]	72	General anesthesia	Lower extremity Systolic pressure*2	IL-6(-), IL-10(-), TNF-α(-), TNF-1β(-)
Pulmonary resection[10]	216	General anesthesia+ intravertebral anesthesia	Upper extremity 200mmHg	IL-6(↓), TNF-α(↓)
Cholecystectomy[14]	20	Intravertebral anesthesia	Lower extremity systolic pressure +100mmHg	IL-6(-)
Colon surgery[32]	90	General anesthesia	Upper extremity 200mmHg	TNF-α(↓), TNF-1β(↓)
Shoulder surgery[37]	63	General anesthesia	Upper extremity 200mmHg	IL-6(-), IL-10(-), TNF-1β(-)
Pancreatic surgery[39]	90	General anesthesia+ intravertebral anesthesia	Upper extremity 200mmHg	IL-6(-)

Notes: "-", no significant difference change; "↓", significant decrease.

Others

Vagal Nerve

The neuroprotective function of stimulating the parasympathetic nerve, particularly the vagal nerve, was shown in experimental experiments using a rat stroke model.[49,50] Enko et al[51] provided evidence of the role of parasympathetic output in RIPC through a human study. Both opioid preconditioning and distant preconditioning may involve the activation of the same pathway in which the vagal nerve plays a crucial role. The vagus nerve provides innervation to numerous essential organs, including the heart, liver, and gut. Additionally, it plays a role in regulating the immune response by inducing an anti-inflammatory profile.[48] Therefore, we hypothesized that the vagal nerve may be involved in postoperative analgesia in RIPC patients. According to a recent study, the cardioprotective effect of RIPC was eliminated when total subdiaphragmatic vagotomy, gastric vagotomy, and selective sectioning of the posterior gastric branch were performed.[51] This finding suggests that the posterior gastric branch of the vagal nerve may play a crucial role in the innervation of circulating factors induced by RIPC.

Endocannabinoids

Endocannabinoids (ECBs) are important circulating factors involved in the analgesic effect of RIPC.[52] ECBs inhibit nociceptive processing by stimulating cannabinoid receptors type 1 (CB1) and type 2 (CB2). One potential mechanism by which they could aid in the alleviation of postoperative pain is through the restriction of p38 phosphorylation, which consequently impedes proinflammatory signaling among spinal astrocytes. Endocannabinoids (ECBs) have a significant impact on the management of acute pain conditions.[53] Furthermore, their levels are increased at different locations within nociceptive pathways in patients with chronic pain,[54–56] underscoring their function as naturally occurring pain-relieving substances. Cannabinoids can reduce opioid analgesic doses,[57] and we boldly speculated that postoperative analgesia resulting from RIPC might be related to endocannabinoids. There is evidence to confirm that the endocannabinoid system within each of these medial prefrontal cortex (mPFC) subregions may be an important factor contributing to the differential regulation of fear-related and pain-related behavior.[58] Collectively, RIPC may facilitate the secretion of one or more circulating factors with protective effects. Additionally, there may be a correlation between the neuronal and humoral pathways, and further investigation is required to elucidate the precise mechanism by which the analgesic effects are exerted.

Glial Cells

Neuropathic pain is pain caused by damage to the nerve as a result of a lesion or disease. In rats that underwent partial sciatic nerve ligation, the administration of RIPC via different routes for five days improved thermal hyperalgesia and mechanical allodynia, and this effect was strongest in the intravenous treatment group. Substances that act against thermal hyperalgesia are relatively present in the serum without ischemic conditioning and increase following RIPC. However, the activity of both glial cell types decreased, especially in the intravenous treatment group; thus, both cell types appear to play a role in the effect of RIPC. In addition, RIPC treatment may also act by increasing Schwann cell remyelination.[59]

Conclusion

Postoperative pain is inflammatory and nociceptive, resulting from the interaction between tissue damage and the stimulation of nociceptive receptors through inflammatory mediators. RIPC reduces inflammation by upregulating the expression of cytoprotection-related genes and downregulating expression of inflammation-related genes associated with the pathogenesis of ischemia–reperfusion injury. The surgical stress response leads to hypercoagulability, endothelial dysfunction, immune dysfunction, and activation of the sympathetic nervous system. RIPC leads to the activation of systemic anti-inflammatory mechanisms, reduces the occurrence of surgical stress response and postoperative complications, and endogenous opioids may also be released, achieves postoperative analgesia, reduces the consumption of morphine and shortens the length of hospital stay.

In the face of the opioid crisis, it is crucial to explore noninvasive nondrug analgesia methods. RIPC can not only provide protection to vital organs but also alleviate postoperative pain and reduce the use of opioids, undoubtedly providing more possibilities for postoperative analgesia programs. However, at present, there are few studies on the

application of RIPC in clinical analgesia, and its mechanism of action needs to be further studied. A large sample size and multicenter study are needed to obtain conclusive results.

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