EXPERT OPINION

Continuous regional anesthesia and inflammation: a new target

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ABSTRACT

Inflammation can be defined as the host response when confronted with an aggression. The purpose of the inflammatory reaction is the defense of the host for re-establishing the baseline homeostasis of the organism. Compared to the neuroendocrine changes associated to the stress response to injury, the inflammatory reaction is the major determinant of patient's recovery in the perioperative period. Perioperative inflammation is involved in the occurrence of various postoperative adverse outcomes other than only acute pain. By consequence, perioperative strategies which limit or control the inflammatory response might have beneficial effects on patient's recovery. The present review summarizes the current knowledges on the interactions between some of these strategies, specifically regional anesthesia (RA) techniques, and inflammation in the context of perioperative medicine. Regional anesthesia through its components i.e. local anesthetics and analgesic adjuvants like alpha-2 adrenergic agonists (clonidine, dexmedetomidine) modulates the inflammatory response consecutive to tissue injury by various mechanisms, at different levels. While experimental studies have shown that RA techniques modulate both local and systemic inflammatory reactions, in contrast, clinical findings are inconsistent as actual RA techniques fail to impact major patients' outcomes beyond immediate postoperative analgesia. The discrepancy between experimental findings and clinical observations asks questions and argues for a different view of perioperative inflammatory processes, in other words for an individualized management of the patients. Future developments of tools to quantify inflammatory and immune profile of patients might certainly lead to exciting findings and to major improvements in perioperative medicine.
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Key words: Inflammation - Perioperative care - Anesthesia.

Perioperative inflammation: physiology and clinical consequences

Inflammation can be defined as the host response when confronted with an aggression. The purpose of the inflammatory reaction is the defense of the host for re-establishing the baseline homeostasis of the organism. Deficiencies or excesses of the inflammatory response cause morbidity and shorten lifespan.[1, 2]

Inflammation is a complex phenomenon which involves many cells and mediators, both locally and systemically. Local mediators like cytokines synthetized at the site of tissue injury help to destroy infective agents, to prevent further tissue damage and to activate wound healing. Inflammation and pain are interrelated as the local release of proinflammatory mediators also leads to peripheral sensitization, hence, pain augmentation (*i.e.* hyperalgesia). Some mediators are released into the circulation where they will induce a systemic inflammatory response (SIR) and act on distant organs *e.g.* interleukin (IL)-6 which will induce the synthesis of acute-phase response proteins in the liver. Some others like interleukin (IL)-1β crosses the blood brain barrier and will induce a state of inflammation, "neuroinflammation", into the central

nervous system (CNS). Microglia (the immune cells of CNS) is first activated then astrocytes (the support cells of neurons), those later showing a durable activation.[3] Neuroinflammation is one of the mechanisms underlying central sensitization process.[3] Whether acute inflammation is essential for recovery from tissue injury, when it persists, inflammatory processes underly both the development and the maintenance of chronic diseases like atherosclerosis, cancer, dementia, obesity, asthma, chronic pain.[2] Because of the deleterious consequences of uncontrolled inflammation, the inflammatory response is a highly regulated process. Termination of the inflammatory reaction is no more seen as a passive process by elimination of local pro-inflammatory mediators but is considered as an active process which involves the synthesis of specific pro-resolving mediators (*e.g.* resolvins, protectins, maresins…) stimulating the resolution without immune suppression.[2]

Tissue lesions combined to anesthesia drugs and techniques are responsible for the important inflammatory reaction and the suppression of cell-mediated immunity observed during the perioperative period.[1] Compared to the neuroendocrine changes associated to the stress response to injury, the inflammatory reaction is the major determinant of patient's recovery in the perioperative period. Perioperative inflammation is involved in the occurrence of various postoperative adverse outcomes other than acute pain:[4] persistent pain, fatigue and delirium, cardiovascular events, cancer recurrence. By consequence, perioperative strategies which limit or control the inflammatory response might have beneficial effects on patient's recovery. The purpose of the present review is to summarize the current knowledges on the interactions between some of these strategies, specifically regional anesthesia (RA) techniques, and inflammation in the context of perioperative medicine (Figure 1).

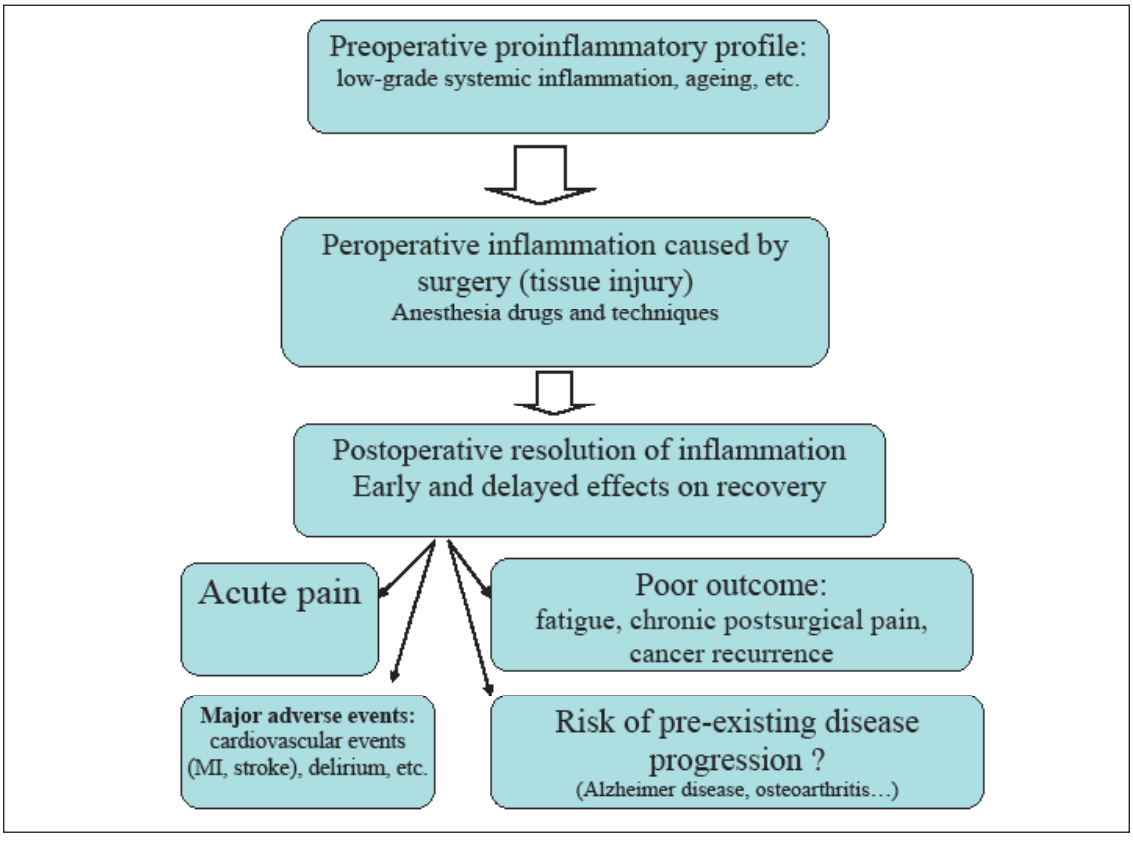

Figure 1.—Consequences of perioperative inflammation.

Mechanisms by which RA modulates the perioperative inflammatory response

RA is a very popular technique, used alone or more frequently, in combination with general anesthesia to provide satisfactory postoperative analgesia in major thoracoabdominal and orthopedic procedures. To date, however, the benefits of RA with regards to perioperative morbidity and mortality reduction continue to be debated.[5] Further, the benefits on later outcomes which are far different than postoperative pain control and which will condition patient's rehabilitation and return to preoperative situation are not clear.[5] As previously mentioned, individual's inflammatory response plays a major role in most if not all of these outcomes. Whether the impact of RA on the inflammatory response has been studied in various experimental models, well-designed clinical studies are scarce bringing unconclusive results. Nevertheless, without doubt, RA can modulate the inflammatory response consecutive to tissue injury by various mechanisms, at different levels.

Local anesthetics (LAs) are the major component of RA techniques. The most cited anti-inflammatory mechanism of LAs is the interruption of nociceptive transmission at the injury site and the reduction of "neurogenic inflammation". LAs block transmembrane proteins voltage-gated sodium channels on nociceptors sensitized by locally released pro-inflammatory mediators (prostaglandins E2, interleukins, etc.). Small-diameter primary afferent fibers when sensitized also release pronociceptive neuropeptides (substance P, CGRP, neurokinin) within their immediate vicinity through an axon reflex mechanism. By consequence, reduction of neurogenic inflammation by LAs will modulate both peripheral and central sensitizations processes as local neurogenic inflammation participates to the general inflammatory response.[6]

Besides, LAs also possess intrinsic anti-inflammatory properties of which all the mechanisms are not completely elucidated yet but differ from that of sodium channels blockade.[7] LAs modulate various steps of the inflammatory cascade as summarized in Table I. In the context of RA techniques, LAs may act on regular immune cells e.g. macrophages recruited on injury site as well as they may interact with resident cells like keratinocytes and fibroblasts which are critically involved in local inflammatory and healing processes.[8, 9] Furthermore, when used for RA, LAs may also be absorbed into the systemic circulation. LAs attenuate the excessive inflammatory response without impairing the physiological host defense in contrast with other immunosuppressant drugs.[10] Leucocytes have no sodium voltage-dependent channels yet their immune function is influenced by LAs at more than one level. Priming of leucocytes is currently considered as playing a major role in the "overstimulation" of inflammatory pathways. The majority of inflammatory mediators (tumor necrosis factor –TNF-α, lipopolysaccharide [LPS], platelet activating factor [PAF], interleukin [IL-8]) signal through G-protein coupled receptors to enhance the response of leukocytes. LAs significantly attenuate G-protein mediated human neutrophil priming,[11] the most potent inhibition being achieved by ester compounds and being inversely correlated with the octanol-buffer coefficient of the LA. Among other mechanisms involved in the anti-inflammatory effect of LAs, protection of the endothelial barrier reduces neutrophils adhesion and endothelial hyperpermeability causing major organ dysfunction. Both ropivacaine and lidocaine effectively block pro-inflammatory TNF-α signalling in endothelial cells.[12] This

Table I.—*Mechanisms involved in modulation of inflammation by local anesthetics and analgesic adjuvants.*

Effects on PMN	Effects on the production of proinflammatory cytokines
↓ leukocyte adherence	↓ NF-kB signaling
↓ migration through the endothelium	↓ the axonal transport of TNF α
↓ phagocytosis	↓ the TNF α receptor expression in DRG
↓ ICAM-1expression	↓ PG biosynthesis and the release of TX B2 and LT B4
↓ the release of chemo-attracting agents	↓ synthesis of IL1 α, IL 1 β, IL 2, IL 8
↓ superoxide anion production of PAF-primed PMN	↓ synthesis of TNF α, IFN ϒ

mechanism may provide therapeutic benefit in acute inflammatory conditions including in the context of carcinologic surgery.[10] It is also worth noting that LAs, specifically lidocaine, modulates central neuroinflammation by decreasing the production of proinflammatory cytokines by microglial cells.[13]

Analgesic adjuvants used in RA techniques may also interfere with the inflammatory reaction at different levels. Among these adjuvants, α2-adrenergic agonists clonidine and more recently dexmedetomidine have been the most studied. Their capacity to modulate the inflammatory response caused by tissue injury mainly relies on α2-adrenergic receptors binding on stimulated proinflammatory cells like macrophages and leucocytes,[14] yielding to reduction of the expression of Toll-like receptors (TLR) 4, hence to reduced activation and translocation of nuclear transcription factor NF-κB and subsequent decrease of pro-inflammatory cytokines production (Table I).[15, 16]

How different RA techniques affect the perioperative inflammatory response in animal models and clinical conditions

Two important concerns need to be raised preliminary. First, the relevance of the animal models used to the mimic clinical conditions. Carrageenan injection, *i.e.* a chemical irritant, is a pure inflammatory model not really representative of incisional pain. More, it is mandatory to take into account major immune differences between rodents and humans, yielding to consider with caution extrapolation of animal data to patients. Second, inflammatory parameters in the majority of clinical studies are biased by the concommittant use of drugs which interfere with the immune and inflammatory responses. The most examplative is the administration of high doses of opioids in control groups without RA. Opioids display imuno-supressive effects and proinflammatory responses in the central nervous system likely via activation of microglia.[3] By consequence, better outcomes for the patients who benefit of RA could actually be translated as better outcomes for patients with no or less opioid intake (*i.e.* balanced anesthesia using opioid sparing regimens). So more studies should be performed, comparing RA with either opioid-sparing or opioid-free general anesthesia in order to state a clear anti-inflammatory effect of RA techniques. A recent review on preventive analgesia by local anesthetics administered by either peripheral nerve blocks or intravenous route suggests that the significant analgesic and antihyperalgesic effect occurs for their use during the postoperative period.[17] It is worth noting that other outcomes different from only acute pain control have not be considered here and that, the intraoperative use of RA is mandatory to maximize the opioids sparing effect, hence the anti-inflammatory effect, of the technique.[18]

With RA, LAs are partly absorbed in the systemic circulation. For anti-inflammatory effects of systemic LAs, special attention has been attributed to intravenous lidocaine administration, particularly in major abdominal surgery. Postoperative ileus and systemic inflammation caused by surgery increase intestinal epithelial permeability which are associated with bacterial translocation and contribute to multiple organ failure. Meta-analysis have confirmed the early benefits of intravenous lidocaine in patients undergoing abdominal procedures but surprisingly not in those undergoing other types of surgeries like cardiac or orthopaedic procedures (Table II).[19]

As intravenous lidocaine is also called "the poor man's epidural", it is interesting to determine the benefit related to the use of neuraxial blocks. In experimental conditions, epidural bupivacaine attenuates mesenteric ischemia-reperfusion related inflammatory response and intestinal damage.[20] Epidural lidocaine anesthesia also reduces endotoxin-induced gut epithelial injury by decreasing monocytic extravasation and intestinal nitrosative stress.[21] In patients undergoing colonic surgery, thoracic epidural analgesia with lidocaine provides better postoperative pain relief and opioid sparing effect, earlier return of bowel function and lesser production of inflammatory cytokines than intravenous lidocaine during 72 hours.[22] The greater benefit of epidural lidocaine over systemic lidocaine certainly questions the role of the central sympathetic nervous system in controlling the systemic

Table II.—*Modulation of perioperative inflammatory reaction by local anesthetics in experimental and clinical conditions: comparison of RA and systemic administration.*

		Clinical parameters		Biological parameters		
		Edema, redness	Pain, hyperalgesia	Local cytokines	Systemic cytokines	Spinal PGE2
Abdominal visceral surgery						
Laparotomy model – rat [34]	CWI ropivacaine	NA	+	0	0	NA
	Systemic ropivacaine	NA	+	+	++	NA
Laparotomy – human [22]	Epidural lidocaine	NA	++	NA	++	NA
	Intravenous lidocaine	NA	+	NA	+	NA
Orthopedic limb surgery						
Carrageenan model – rat [29, 30]	PNB bupivacaine	+	++	+	++	+
	Systemic bupivacaine	0	0	0	++	0
Knee arthroplasty – human [31, 32]	PNB bupivacaine / ropivacaine	+	++	0	0	NA

RA: regional anesthesia; CWI: continuous wound infusion; PNB: peripheral nerve block.
(+) positive modulatory effect of inflammatory parameters i.e. reduction of inflammation; (0) no modulatory effect of inflammatory parameters.
NA: data not available.

inflammatory response.[23] Regional sympathetic block increases intestinal perfusion. Further, the sympathetic nervous system shows overactivity under stress conditions *i.e.* surgical trauma and RA may help to modulate this overeactivity and to re-establish the immune balance in the perioperative period. Most of the studies assessing the anti-inflammatory effect of neuraxial anesthesia and analgesia have compared the combination of epidural with general anesthesia to general anesthesia alone. The results have been disappointing, showing only partial and temporary effect on the acute inflammatory stress response in term of cytokines expression.[24] Spinal anesthesia exhibits perioperative anti-inflammatory properties that seem to be moderate and transient when compared with epidural anesthesia. Spinal anesthesia is often used for relatively short lasting procedures. By example, in patients undergoing knee arthroplasty, no difference was found regarding systemic modulation of the inflammatory response between spinal anesthesia followed by systemic morphine analgesia and epidural anesthesia followed by postoperative epidural analgesia.[25] Regarding the analgesic adjuvants, it is well known that α2-adrenergic agonists blunt central sympathetic outflow. Compared with epidural bupivacaine, epidural clonidine demonstrates greater anti-inflammatory effects (reduction of systemic proinflammatory cytokines expression) after colorectal surgery, what lets suppose that the modulation of the sympathetic nervous system effectively plays a role in controlling the SIR as aforementioned.[26, 27] More, the reduction of the sympathetic outflow may increase the role of the parasympathetic system. The cholinergic anti-inflammatory pathway through the stimulation of the vagus nerve is a well-known mechanism of neural inhibition of inflammatory response. Acetylcholine, the principal neurotransmitter of the vagus, dose-dependently inhibits the release of pro-inflammatory cytokines by macrophages.[28]

A series of experimental studies using the carrageenan model of peripheral inflammation in rats have questioned the anti-inflammatory properties of peripheral nerve blocks.[29] The authors have demonstrated that LAs act at different levels when administered systemically or via a nerve block. To summarize, LAs peripheral nerve blocks decrease both paw edema and hyperalgesia caused by local tissue inflammation, even when the nerve block is performed on the contralateral limb. Systemic absorption of LAs partly may explain the anti-inflammatory effect of a contralateral nerve block. Both systemic administration of LAs and perineural one reduce the systemic inflammatory response (SIR) while systemic LAs have no effect on paw edema and local hyperalgesia.[30] Spinal increase of prostaglandin (PG) E2 correlates with pain and hyperalgesia after tissue injury in animal models and

clinical situations.[4] After hindpaw carrageenan injection, bupivacaine sciatic block inhibits COX-2 expression in both dorsal root ganglion and spinal cord, leading to a reduction of spinal PGE2, while systemic bupivacaine administration does not modify COX-2 expression.[30] In humans, the anti-inflammatory effects of peripheral nerve blocks have been explored after major orthopaedic procedures like knee arthroplasty.[31, 32] Despite the use of continuous nerve blocks with bupivacaine or ropivacaine, the inflammatory parameters *i.e.* systemic and local cytokines expression were not really affected while knee edema, early postoperative pain and mobilization were improved in the block groups. Peri-neural administration of clonidine in the context of nerve injury reduces the development of hypersensitivity by altering the balance of pro- and anti-inflammatory cytokines locally released during the process of Wallerian degeneration.[14] Drug effect is mediated through binding to α2-adrenergic receptors expressed on local macrophages. Similar findings have been recently reported for dexmedetomidine, which is more selective for α2-adrenergic receptors than clonidine.[15] Here, it is interesting to mention that systemic administration of clonidine improves posthypoxic endothelial function and modulates inflammation during limb reperfusion in both animal models and healthy volunteers.[33]

Wound infiltration is a non-invasive, easy technique often considered as useful adjunct to multimodal analgesia for postoperative pain management as it reduces pain and shows an opioid sparing effect. The catheter location is important because of the role played by deep structures into postoperative pain *e.g.* deep muscular layers, peritoneum. Today, pre-peritoneal infusion of LAs is considered as an alternative to epidural analgesia for abdominal procedures. Using an animal model of laparotomy, Kfoury *et al.*[34] have tried to explain the mechanisms of action involved in intrawound LAs analgesic effect. They have demonstrated that both high doses of preperitoneal infusion of ropivacaine and systemic ropivacaine similarly reduced mechanical and visceral sensitivity while systemic administration alone was associated with an anti-inflammatory effect (reduced stimulated production of TNF-α and IL-1β in whole blood and peritoneal macrophages cultures). In humans, there is a lack of correlation between systemic *i.e.* serum levels and local expression of intra wound cytokines and PGs after caesarean section.[8] In the same clinical model, continuous intrawound infusion of bupivacaine seemed to enhance the local proinflammatory response while showing clinical analgesic effects [9]. Recent experimental data have highlighted the proinflammatory effect of bupivacaine on peripheral nerve and the protective effect of the α2-adrenergic agonist dexmedetomidine in that setting.[35] Moreover, local injection of dexmedetomidine counteracts the inflammatory reaction caused by intraplantar carrageenan in rats as it reduces paw edema, leucocytes activation and decreases the local production of TNF-α and the local expression of COX-2.[36]

RA, inflammatory response and patient's outcomes in clinical practice

While it is clear from experimental data that RA display anti-inflammatory and immunologic modulatory properties, in clinical practice the impact on perioperative inflammation is not so evident. First, there is clearly a dissociation between the clinical effects reported (*i.e.* reduction of local edema and acute pain) and the modulation of the biologic markers of inflammation (*i.e.* local cytokines expression), particularly in orthopaedic setting. Second, RA benefits in term of patients' major outcomes, other than acute pain control (*e.g.* persistent pain and cancer recurrence) are unconclusive. Epidural anesthesia and paravertebral block, respectively, may prevent persistent postsurgical pain after thoracotomy and breast surgery in about one out every four to five patients.[37] In orthopedic procedures, where long-lasting preoperative pain and inflammation are very common, the benefits are even less evident as 4-days continuous peripheral nerve blocks only improve rehabilitation at 6 weeks after hip or knee arthroplasty but not later and do not prevent the development of persistent pain.[38] Inflammation not only plays a central role at different stages of tumor development but also contributes to the initiation of antitumoral

immune response.[39] In regard to that complex situation, it is not surprising that systematic reviews based on retrospective studies have found little evidence to support major benefit of RA on survival after oncologic surgery.[40, 41]

Unsolved issues and questions deserving future research in the field

The poor clinical results certainly incite us to question the reasons for RA failure to influence longterm outcomes. First, the severity and the duration of ongoing perioperative inflammatory processes may differ from one individual to the other. Experimental data have clearly shown that a prolonged nerve block is necessary to decrease the systemic consequences of the local inflammatory reaction [6] as well as only repeated perineural injections of clonidine modulate local cytokines expression yielding to longlasting decrease of hypersentisivity [14]. Under clinical conditions, prolonged peripheral nerve blocks *i.e.* lasting longer than the usual postoperative duration (2 to 4 days) might be necessary to control perioperative inflammation and to demonstrate beneficial effect on patient's outome as demonstrated in the context of limb amputation (median duration of sciatic block of 30 days; extreme values 3 to 80 days).[42] Second, studies have not taken into account the preoperative basal status of the patients while several preoperative conditions are "inflammatory prone" like asthma, obsesity, rheumatoid arthritis, inflammatory bowel diseases, what could have blunted the impact of some RA techniques. The widespread use of ultrasounds has contributed to RA success in both acute and chronic pain settings. In the perioperative period, the anti-inflammatory impact of techniques like TAP block has not yet been assessed. Furthermore, when used for RA, LAs may also be absorbed into the systemic circulation. The use of ultrasound-guided RA has led to a decrease in the volume of LAs administered, reducing not only the risk of systemic toxicity but perhaps also blunting expected benefits of LAs systemic concentrations. Finally, clinical observations also question the value of clinical markers currently used to quantify RA effect on the perioperative inflammation as major discrepancies between local and systemic expression of common cytokines are usually noted, and clinical reduction of pain and inflammation does not really correlates with decrease in biological makers.[31, 32] Such inflammation-based scores are already used to assess the prognostic of cancer patients [43] but prospective studies aimed to validate them in perioperative situations are currently missing. It is also interesting to note that RA impact on the mediators involved in the active resolution of inflammation has not yet been assessed.[2]

Conclusions

Compared to the neuroendocrine changes associated to the stress response to injury, the inflammatory reaction is the major determinant of patient's recovery in the perioperative period. Uncontrolled inflammation is involved in the majority of adverse outcomes after surgery. Experimental studies have shown that RA techniques using LAs and analgesic adjuvants modulate both local and systemic inflammatory reaction caused by surgical injury. In contrast, clinical findings are inconsistent as actual RA techniques fail to impact major patients' outcomes beyond immediate postoperative analgesia. The discrepancy between experimental findings and clinical observations ask questions and argues for a different view of perioperative inflammatory processes, in other words for individualized management of the patients. Future developments of tools to quantify inflammatory and immune profile of patients might certainly lead to exciting findings and to major improvements in perioperative medicine.

Key messages

— Local anesthetics (LAs) are the major component of RA technique. LAs-related anti-inflammatory mechanisms involve both the interruption of nociceptive transmission (reduction of neurogenic inflammation) and intrinsic anti-inflammatory properties unrelated to sodium channels blockade (direct action on immune cells). By contrast with

immunosuppressant drugs, LAs attenuate the excessive inflammatory response without impairing the physiological host defences.

— RA-related modulation of perioperative inflammation also relies on a well-known perioperative opioid-sparing effect as opioids display immuno-suppressive and pro-inflammatory properties. To state a clear anti-inflammatory effect of RA techniques, well-designed studies should compare RA with opioid-sparing general anesthesia.

— Analgesic adjuvants used in combination with LAs in RA also possess intrinsic anti-inflammatory and immune-modulatory properties (*e.g.* alpha-2 adrenergic agonists clonidine and dexmedetomidine).

— Clinical observations mainly demonstrate the anti-inflammatory modulatory effects of RA as a reduction of acute postoperative pain and hyperalgesia although the relationship between clinical markers of the inflammatory reaction and biological ones remains unclear. Anti-inflammatory impact on major delayed outcomes like persistent pain, cancer recurrence, progression of inflammatory diseases… is still unknown and mostly unexplored.

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