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ABSTRACT

The inflammatory response is an important determinant of outcome after major surgery. Perioperative excessive stimulation of the inflammatory and haemostatic systems plays a role in the development of postoperative ileus, ischaemia-reperfusion syndromes (e.g. myocardial infarction), hypercoagulation syndromes (e.g. deep venous thrombosis) and pain; together, these represent a significant fraction of major postoperative disorders. Epidurally administered local anaesthetics prevent or modulate many of these processes. Since local anaesthetics show inflammatory modulating properties *in vitro* and *in vivo*, they also might prevent these postoperative inflammatory processes when administered intravenously. Indeed, clinical studies have shown that perioperative local anaesthetic administration significantly reduces the incidence of thrombosis and postoperative pain, shortens postoperative ileus and decreases hospital stay. These findings suggest that intravenous administration of local anaesthetic perioperatively might prevent or reduce several postoperative disorders resulting from excessive stimulation of inflammatory and haemostatic systems, and thereby improve surgical outcome.

INTRODUCTION

Surgery elicits broad alterations in haemodynamic, endocrine-metabolic and immune responses. The inflammatory response is essential for structural and functional repair of injured tissue, as complement, granulocytes, macrophages and many other mediators are required for appropriate wound healing. However, excessive stimulation of inflammatory cascades may aggravate tissue damage. This occurs, for example, in reperfusion injury after hepatectomy or myocardial ischaemia during cardiac surgery. In certain populations of patients, excessive inflammatory stimulation may lead to host auto-injury inflammatory syndromes (e.g. SIRS and ARDS), sepsis, multi-system organ failure (MSOF) and eventually death. In a much greater proportion of the surgical patient population, postoperative pain and postoperative hypercoagulation represent significant morbidity due to excess activation of inflammatory responses. Since these responses are initiated during surgery, intraoperative interventions might decrease their frequency and severity.

Epidural administration of local anaesthetics was designed to provide intraoperative anaesthesia and postoperative analgesia. However, in recent years it has become clear that epidurally administered local anaesthetics have benefits far beyond anaesthesia and pain relief; indeed, the technique has significant impact on the outcome of major surgical procedures. A recently published meta-analysis concluded that neuraxial anaesthesia using local anaesthetics decreased overall mortality by approximately one third, reduced the odds of deep vein thrombosis by 44%, pulmonary embolism by 55%, transfusion requirements by 50%, pneumonia by 39%, and respiratory depression by 59%. There were also reductions in myocardial infarction and renal failure [1]. In addition, epidural anaesthesia using local anaesthetics has been shown to attenuate the endocrine and metabolic response to upper abdominal surgery, to reduce postoperative ileus, and to shorten duration of intubation and intensive care stay in patients undergoing abdominal aortic operations. We will refer to these actions as “secondary effects” of epidurally applied local anaesthetics.

Since placement of the epidural catheter is not without risk and some discomfort for the patient, a considerable number of patients reject this anaesthetic technique. In addition, it is not suitable for use under all conditions (e.g. in anticoagulated patients) or for all types of surgery (e.g. neurosurgery or surgery where an epidural catheter has to be placed higher than the thoracic level, for example in some types of orthopaedic surgery). However, most of the “secondary effects” attained when using epidural anaesthesia with local anaesthetics have recently been demonstrated to occur also when local anaesthetics are administered by other routes. The underlying mechanism for these beneficial actions is most likely an inflammatory modulating action of local anaesthetics. This suggests that (in contrast to classic epidural anaesthesia and analgesia) these beneficial effects do not depend on blockade of spinal nerves, but instead on systemic levels of local anaesthetics resulting from systemic absorption of the drug from the epidural space. If these protective effects could indeed be achieved after intravenous administration of local anaesthetics (or derivatives), this would provide a

convenient and safe approach to preventing inflammatory postoperative disorders, and would be likely to impact perioperative medicine significantly. In addition, intravenous application of local anaesthetic provides an easier and safer route compared with epidural administration. This would be especially relevant for patients not eligible or willing to receive an epidural catheter. One should not expect that intravenously applied local anaesthetics are able to mimic all beneficial effects obtained after epidural administration. For example, segmental nerve block leading to insensitivity to pain in the operating field or sympathetic blockade will not be achieved by systemic application of these drugs. Nonetheless, patients not willing or able to receive an epidural catheter might benefit when general anaesthesia is supplemented by infusion of local anaesthetics.

In the remainder of this article, we will discuss the following statements:

- Local anaesthetics administered intravenously prevent excessive stimulation of the inflammatory response.
- Postoperative thrombosis (due most likely to surgery-induced hypercoagulability) is significantly reduced after either epidural or intravenous local anaesthetic administration, as compared with general anaesthesia.
- Postoperative ileus is reduced after either epidural or intravenous local anaesthetic administration as compared with general anaesthesia.
- Length of stay in the hospital is reduced after systemic application of local anaesthetics, as compared with general anaesthesia.
- Postoperative cognitive dysfunction is reduced by intravenous application of local anaesthetics, as compared with general anaesthesia without administration of local anaesthetics.

In addition, we will discuss some of the molecular mechanisms underlying these beneficial effects.

LOCAL ANAESTHETICS PREVENT EXCESSIVE STIMULATION OF THE INFLAMMATORY RESPONSE

Local anaesthetics modulate the inflammatory response *in vivo* [2]. They prevent or reduce inflammatory disorders, such as reperfusion injury in heart [3]. Similar effects have been reported in lung and brain. Local anaesthetics mitigate endotoxin- or hyperoxia-induced pulmonary injury [4, 5]. Beneficial effects of local anaesthetic treatment in inflammatory bowel diseases are well documented [6, 7]. In contrast to corticosteroids, which depress the inflammatory response and impact negatively on postoperative outcome, local anaesthetics selectively inhibit only overactive responses of the inflammatory and haemostatic systems without affecting normal function [8, 9]. This property makes them unique therapeutics. As a result, and in major contrast to corticosteroids, local anaesthetics decrease inflammation without increasing the susceptibility to infections, and prevent postoperative thrombotic events without increasing bleeding.

LOCAL ANAESTHETICS PREVENT POSTOPERATIVE THROMBOSIS

Already 30 years ago it was demonstrated that intravenous lidocaine effectively prevents postoperative thrombotic events, without increasing bleeding [10]. Further studies supporting the antithrombotic effects of local anaesthetics are summarized in recently published reviews [11]. Most of these effects are similar to those obtained after epidural administration of local anaesthetics, and can potentially be explained by an anti-inflammatory effect of local anaesthetics. That the effects are likely due to systemic absorption, and not to neuraxial block, is suggested by findings that epidural anaesthesia using local anaesthetic (leading to neuraxial blockade plus significant plasma local anaesthetic concentrations) prevents surgery-induced hypercoagulation [9], whereas spinal anaesthesia (leading to neuraxial blockade but no significant plasma local anaesthetic levels) does not affect coagulation.

LOCAL ANAESTHETICS REDUCE POSTOPERATIVE ILEUS AND DURATION OF HOSPITAL STAY

Postoperative ileus results from a sterile inflammation of the peritoneum after bowel manipulation. A double-blinded prospective randomised study in patients undergoing radical prostatectomy showed that continuous intravenous administration of lidocaine (intra-operatively and for 2 h postoperatively) led to a significant reduction in postoperative analgesic consumption, more rapid return of bowel function, and a shortened hospital stay [12]. Effects of epidurally administered local anaesthetics on postoperative ileus are similar, and have been reviewed extensively.

LOCAL ANAESTHETICS ARE NEUROPROTECTIVE

Recent findings demonstrate a neuroprotective effect after intravenous administration of local anaesthetics, leading to significant reduction in cognitive dysfunction after cardiac surgery [13]. Recent animal data demonstrating significant neuroprotective effects of low concentrations of local anaesthetics support these clinical results [14].

MECHANISMS OF ACTION

The cellular substrate for these actions is likely to reside, in part, in the fact that priming, but not activation, of neutrophils is inhibited by local anaesthetics [15, 16]. Priming refers to a process whereby the response of neutrophils to a subsequent activating stimulus is potentiated. Release of oxygen metabolites is markedly enhanced when neutrophils have previously been primed. The priming process has been shown to be a critical component of neutrophil-mediated tissue injury both *in vitro* and *in vivo* [17], and inhibition of this process by local anaesthetics would be expected to reduce such injury. The mechanisms underlying these actions of local anaesthetics on priming have not been elucidated in detail, but selective inhibition of Gq protein function by local anaesthetics has been demonstrated recently [18]. Since Gq is important for many inflammatory and haemostatic signalling pathways, the effects of local anaesthetics might be explained at least in part by functional inhibition of Gq protein. Offermanns et al. reported that platelets from mice deficient in the α -subunit of Gq are unresponsive to a variety of physiologic platelet activators [19]. As a result, these mice are protected from collagen and adrenaline-induced thromboembolism. The authors concluded that the Gq protein may thus be a new target for drugs designed to block the activation of platelets. The antithrombotic actions of local anaesthetics might result in part from inhibition of Gq protein function in platelets.

CONCLUSIONS

In summary, there is strong evidence for an inflammatory modulating action of local anaesthetic, and it is reasonable to hypothesise that this effect explains why continuous intravenous administration of these compounds in the perioperative period has several beneficial effects, similar to those obtained with epidural administration. However, the underlying molecular and cellular mechanisms of those actions are not sufficiently understood. Unveiling these mechanisms and applying them to manage the inflammatory response during surgery, could open possibilities for a new, effective therapeutic approach to prevention of postoperative disorders.

In order to reach this point, a prospective randomised partially blinded (epidural versus general anaesthesia studies cannot be done in a double-blinded manner) clinical trial model seems to be appropriate. Such a trial should be performed in patients undergoing general surgical procedures, and would contain three arms: (1) one group of patients receiving epidural anaesthesia, (2) a second group receiving general anaesthesia with supplemental intravenous administration of local anaesthetics to attain blood concentrations similar to those attained using epidural anaesthesia, and (3) a third group receiving general anaesthesia only, with supplemental intravenous administration of saline as control. The target group will depend on the issue to be studied: cognitive dysfunction is probably most appropriately studied in cardiac surgery patients, reduction of postoperative ileus in patients undergoing abdominal surgery, etc. One important endpoint undoubtedly will be duration of hospital stay. As a result, multiple trials are likely to be necessary.

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