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Novel methods of local anesthetic delivery in the perioperative and postoperative setting—potential for fibrin hydrogel delivery☆,☆☆,★

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Abstract The benefits of high-quality postoperative analgesia are well documented and include earlier mobilization, fewer respiratory and cardiovascular complications, and shorter hospital stay. Local anesthesia–based acute pain regimens are at worst equal to and at best superior to opiate-based regimens from the perspective of analgesia. A multimodal approach limiting opioids by combining with local anesthetics has additional beneficial effect on outcomes such as nausea and vomiting, pruritus, gastrointestinal function, respiratory complications, and neutrophil function. Wound catheters providing continuous infiltration of local anesthetics offer a rational approach to effective perioperative analgesia, but their use is limited by a short duration of action. There is an identified need for further methods to optimize longer-acting delivery of these agents. This article reviews current and evolving longer-acting techniques and their limitations with particular focus on the potential advantages of a fibrin hydrogel–based system.

1. Introduction

The benefits of high-quality acute pain management in the perioperative and postoperative setting extend far beyond minimizing the adverse effects of agents used. The negative outcomes of pain include a decrease in vital capacity and alveolar ventilation, pneumonia, tachycardia, hypertension, myocardial ischemia, transition to chronic pain, and insomnia [1-3]. The administration of effective analgesia, a key component of enhanced recovery pathways, has been shown to reduce postoperative morbidity, permit earlier hospital discharge, and increase patient satisfaction [4]. Despite reported improved patient outcomes, more than one-third of patients experience moderate to severe pain in the first 24 hours after their surgery [5]. As a result, the effective delivery of analgesia remains a key concern and focus in clinical practice.

The release of insulin, glucagon, serum cortisol, and several acute phase reactants produces a cascade of hormonal,

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immunological, metabolic, and inflammatory events in response to the physical trauma of surgery. Blunting this surgical stress response can improve cardiovascular, respiratory, coagulation, and gastrointestinal physiology in the perioperative and postoperative period, reducing morbidities and length of inpatient stay [6]. Attenuating this response also positively impacts on cognition and immune function [7]. Opioids are considered to have at best a limited capacity in blunting the physiological response to surgery [8]; however, regional anesthetics have a proven significant impact [7].

Opioid action is the result of combined interaction on 4 subtypes of receptor (delta, kappa, mu, and nociceptin opioid receptors). These receptors are located at many neuraxial sites and also in some peripheral locations [9]. Their use is limited by well-known adverse effects such as respiratory depression, nausea and vomiting, constipation, and itching. However, the negative implications of excessive opioid use extend far beyond these adverse effects.

It is now well established that opioid use can result in immunosuppression and increased susceptibility to infection. There are a number of mechanisms suggested for this modulation of the innate immune system including decreasing the proliferative pathway of macrophage progenitor cells and lymphocytes [10], the modulation of upstream signaling effectors such as cyclic adenosine monophosphate [11], and the inhibition of inflammatory cytokine production such as interleukin-6 [12]. In the context of wound healing, the use of morphine has been proven to delay the cellular events essential to bacterial clearance and wound closure [13]. It is also suggested to have a role in cancer recurrence attributed to its direct action on regulatory T cells through vascular endothelial growth factor receptor 2 and opioid receptors [14].

The transition from acute postoperative pain to persistent postsurgical pain and chronic postsurgical pain is influenced by preoperative, intraoperative, and postoperative surgical, psychosocial, socioenvironmental, and patient-related factors [15]. Although a complex and multifactorial pathway, studies have identified opioid consumption as a potential predictor of this transition. This has been described in the context of long-term use preoperatively [16,17] but also with high-dose consumption in the acute period [18].

These implications have placed a heightened emphasis on acute pain management in the operative setting with focus on a multimodal approach. This involves use of opioids in combination with other agents such as paracetamol, nonsteroidal anti-inflammatory drugs, and regional or local anesthesia to minimize the requirements for opioid therapy [19].

The infusion of local anesthetic at the site of surgical incision offers a rational approach to perioperative analgesia. The placement of bupivacaine-soaked gelatin sponges into wounds has improved postoperative analgesia in obstetric surgeries [20,21]. In more widespread use is continuous wound infusion. There are major advantages of this technique including high analgesic efficacy with technical simplicity, low rate of infection, and limitation of systemic adverse effects [22]. Continuous wound infusion, carried out using a multiperforated catheter placed during surgery predominantly in a subcutaneous or subfascial location, has been effective in general, cardiothoracic, and breast surgery [23]. Despite some disagreement in the literature [24-26], overall, this technique is considered safe and extremely effective; however, the short duration of action of the agents used is considered a limitation [23].

Despite the success of continuous wound infusion, there remains an identified need for further methods to optimize longer-acting delivery of these agents. This review evaluates new and evolving methods with a particular focus on fibrin hydrogel as a potential delivery agent.

1.1. Long-acting local anesthetic agents

Two main approaches have been suggested to prolong the course of local anesthetic agents. The first is the use of long-acting local anesthetics. Currently, etidocaine, bupivacaine, and ropivacaine are the longest-acting agents licensed for clinical use. The development of higher concentrations of these agents is limited by their potential for systemic toxicity and effect on motor blockade. Etidocaine has a profound motor blockade that can outlast sensory blockade [27]. Bupivacaine use is limited by its potential for cardio- and central nervous system toxicity. The introduction of levobupivacaine in the 1990s, the pure S enantiomer of bupivacaine, has improved the safety profile of the drug with its lesser affinity for both myocardial and central nervous centers [28]. However, it is ropivacaine—with its reduced cardio- and central nervous system toxicity and a lower propensity for motor blockade—that has become the agent of choice particularly in peripheral nerve blocks [29].

The use of adjuncts can augment the duration of action of anesthetic agents. Dexamethasone has been successful in this context; however, its mechanisms are poorly understood [30]. There are extensive studies using ropivacaine, lignocaine, and bupivacaine supporting that it can double the duration of analgesic effect of these agents [31]. Although there is no reported optimal length, effective use of local anesthetic infiltration regimens has described at up 72 hours in colorectal surgeries [32] and 55 hours in orthopedic surgeries [33]. Attempting to achieve these considerable time durations has diverted focus to the use of novel techniques to prolong the action of existing local anesthetics. This can be achieved with delivery systems capable of encapsulating the local anesthetic agent and giving sustained release over a prolonged period. The optimal delivery agent should be biocompatible with biocompatible degradation products, biodegradable, cost-effective, and capable of achieving both sustained and predictable drug release (Fig. 1).

As yet, no system fulfills all these criteria. Delivery systems described include hyaluronic acid–based hydrogel, loaded biphasic calcium phosphates, and bioadhesive films. Encapsulating agents have shown the most promise in this regard. Liposomes, polymers, microcapsules, and cyclodextrins (CDs) have been the most extensively evaluated [34].