

Intravenous Lidocaine for Postoperative Recovery After Major Abdominal Surgery

BY MATHIEU SÉRIE, MD

Over the past few years, the concept of fast-track recovery in gastrointestinal (GI) surgery has gained momentum; the objectives are to improve patient comfort, decrease postoperative mortality, shorten hospital stay, and reduce financial costs. To reach these objectives, postoperative recovery must be multimodal, combining the following: optimization of the patient's preoperative physical condition, attenuation of surgical stress, efficient postoperative pain management, early mobilization, and rapid oral food intake. One cornerstone of this concept is based on the administration of local anesthetic agents via a thoracic epidural catheter, which may decrease postoperative pain at rest and during mobilization, and reduce opioid consumption, sympathetic tone, and postoperative ileus.¹ However, the insertion of an epidural catheter is not without risk and some patients do not accept this type of analgesia. Furthermore, this technique cannot be performed under all conditions, particularly in patients receiving anticoagulants or when perioperative coagulation problems are anticipated. For those patients, the administration of intravenous lidocaine could be considered. This issue of *Anesthesiology Rounds* reviews the experimental data on the systemic effects of lidocaine and the clinical studies involving intravenous lidocaine to promote early recovery.

Some of the benefits of epidural anesthesia appear to be due to the systemic absorption of local anesthetics;² in fact, these agents have anti-inflammatory, analgesic, antihyperalgesic, and antithrombotic properties. The systemic administration of local anesthetics thus constitutes a new tool that is both easier and safer to use than an epidural in a fast-track postoperative recovery setting for major GI surgery.³⁻⁸ This mode of administration is particularly indicated in patients for whom epidural anesthesia is impossible, either because of patient refusal, contraindications,⁷ or for procedures where the benefits of epidural anesthesia are marginal or controversial, as in laparoscopic surgery.^{4,9,10}

PROPERTIES OF INTRAVENOUS LIDOCAINE: EXPERIMENTAL DATA

Lidocaine injected close to a nerve interrupts the propagation of the action potential, or nerve impulse, by binding to sodium channels and preventing their activation in response to depolarization. In addition to this well-known effect, lidocaine has anti-inflammatory, analgesic, antihyperalgesic, antithrombotic, and neuroprotective properties, and the mechanisms differ from that of the local anesthetic effect.

Committee for Continuing Medical Education
Department of Anesthesiology
University of Montreal

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Co-editor and Chairman of the Department of Anesthesiology, University of Montreal

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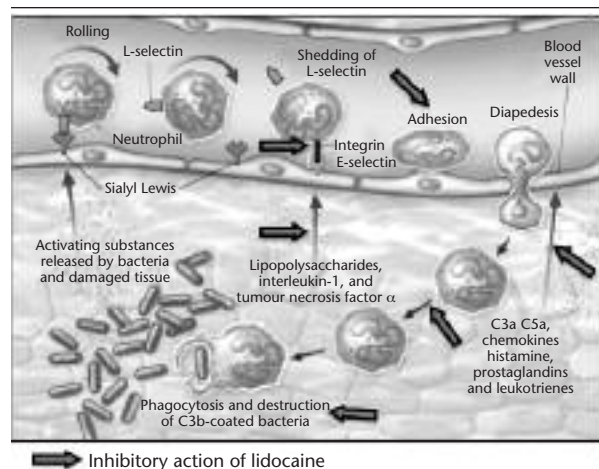
University of Montreal
Department of Anesthesiology
Faculty of Medicine

Université 
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FIGURE 1: The different phases of an inflammatory reaction and the inhibition by lidocaine



Anti-inflammatory properties

Local anesthetics have an effect on inflammatory mediators, neutrophil leukocytes, and macrophages.

Effects on the secretion of inflammatory mediators

Leukotrienes B4 (LTB4) stimulate neutrophil leukocytes and, in synergy with prostaglandin E2, are responsible for the increase in vascular permeability.¹¹ Lidocaine inhibits the release of leukotrienes by inflammatory cells, which explains the diminution of inflammatory edema when local anesthetics are administered. Additionally, lidocaine inhibits interleukin-1 α (IL-1 α) and histamine release. The role of IL-1 α in the inflammatory response is to bind neutrophil leukocyte receptors and thus stimulate phagocytosis and degranulation.¹²

Action on neutrophil leukocytes

Lidocaine inhibits all phases of the inflammatory cell response via various mechanisms (Figure 1):^{2,12}

- Lidocaine decreases the adhesion of neutrophil leukocytes to the endothelium by diminishing the expression of CD11b-CD18 receptors (of the integrin family) on the surface of neutrophils and modifying the morphology of neutrophils.¹³ In a rabbit model, 5 minutes after a 1.5 mg/kg bolus injection, the reduction of granulocyte adhesion reaches 40%; it is reversible after 15 minutes and maintained by a continuous lidocaine infusion.¹⁴

- Lidocaine inhibits the metabolism and mobility of neutrophil leukocytes when used at 4-20 mM concentrations and causes immobilization at concentrations >20 mM, by destroying the integrity of the

cytoskeleton and interacting with the lipid membrane of the cell. Reduced neutrophil adhesion, metabolism, and motility results in a decrease in inflammatory response with fewer neutrophils at the site of inflammation. The final effect is difficult to anticipate and is subject to significant controversy, ie, reduced healing, no change or improved healing, depending on circumstances.

- Local anesthetics inhibit neutrophil leukocyte priming.^{2,12} Neutrophil priming is the process by which the neutrophil response to activation is enhanced. This important process has been demonstrated in tissue injury secondary to neutrophilic action, both *in vitro* and *in vivo*. The mechanism for the inhibition of neutrophilic leukocyte priming is the selective inhibition of Galpha(q) protein by local anesthetics.¹⁵ Galpha(q) protein is also found on platelets and part of the antithrombotic effects of lidocaine could be explained by the inhibition of this protein.¹⁶

- Lidocaine reduces the release of free radicals in a dose-dependent manner.^{2,12}

- Lidocaine reduces phagocytosis by neutrophil leukocytes.

Action on macrophages

Lidocaine inhibits macrophage function by modifying their shape and inhibiting phagocytosis by macrophages *in vitro*.¹²

Analgesic and antihyperalgesic properties

Intravenous local anesthetics have been demonstrated to diminish pain in many situations, particularly those associated with hypersensitivity (eg, fibromyalgia or neuropathic pain). Analgesic and antihyperalgesic properties of lidocaine result from actions that are both peripheral and central. At the peripheral level, lidocaine causes a reduction of tonic firing in peripheral neurons, and an increase in the excitability threshold of Adelta and C nerve fibers at 2-10 μ g/mL concentrations.¹⁷ At the central level, lidocaine inhibits spinal visceromotor neurons, inhibits N-methyl-D- aspartate (NMDA) receptors,¹⁸ and reduces the hypersensitization phenomena (wind-up of action potentials) at the spinal level. In an animal model, lidocaine inhibits the nociceptive effects of abdominal distension in a dose-dependent manner.

Antithrombotic effects

When local anesthetics are administered *in vitro*, inhibition of platelet aggregation induced

by thrombin or collagen can be observed. This effect appears to be proportional to the incubation time and is greater with lidocaine than with other local anesthetics.^{19,20} Additionally, an *in vitro* increase in coagulation time can be noted, as measured by activated coagulation time (ACT) and alterations of thromboelastography (TEG), when bupivacaine is used in plasma concentrations commonly encountered clinically.²¹

Lidocaine also induces inhibition of the Galpha(q) protein of neutrophil leukocytes.¹⁵ The presence of Galpha(q) protein on the surface of platelets and a lack of its subunit in mice appears to have protective effects against thromboembolic events.¹⁶ A clinical study²² from *The Lancet* in 1977 showed that an infusion of lidocaine at 2 mg/min administered for 6 days after hip surgery caused a reduction in the incidence of deep vein thrombosis without increasing bleeding. This suggests that the decrease in thromboembolic events observed during epidural anesthesia is caused by the systemic absorption of local anesthetics and their dose-dependent antithrombotic effects, and not by the neuraxial blockade they produce. This may explain why there is no decrease in thromboembolic events with intrathecal anesthesia, where doses of local anesthetics are lower.²²⁻²⁵

Neuroprotective effects

In an *in vivo* setting, lidocaine has demonstrated protective properties against cerebral ischemia. Lidocaine preserves cerebral function in dogs after deep hypothermic circulatory arrest. It also allows for a reduction in the size of cerebral infarct in a rat model of ischemic lesions. Two clinical studies^{26,27} conducted in patients undergoing cardiac surgery have shown a decrease in the incidence of early cognitive dysfunction in patients who were administered intravenous lidocaine during the perioperative period.

INTRAVENOUS LIDOCAINE FOR POSTOPERATIVE RECOVERY

Lidocaine has been used in clinical trials to decrease postoperative pain and shorten the delay to normal bowel function, while remaining below toxic doses.

Postoperative pain

Opioid agents remain the cornerstone for treatment of moderate-to-severe chronic pain;

however, because of the frequency and consequences of their side effects, many choose to give other analgesics that allow a reduction in the use of opioids. Given its anti-inflammatory, analgesic, and antihyperalgesic properties, lidocaine has demonstrated efficacy as a co-analgesic in major laparoscopic⁴ or open^{3,5,6,8} GI surgery,⁴ at least when initiated at the beginning of the procedure and continued throughout surgery.

Koppert et al⁶ randomized 40 patients undergoing major abdominal surgery via laparotomy (5 surgeons; different surgeries: nephrectomy, colectomy, cystectomy). One group received a lidocaine protocol (1.5 mg/kg bolus at least 30 min before surgical incision, followed by a continuous infusion of 1.5 mg/kg/hr lidocaine until 1 hour after surgery) and the other group a placebo. The results showed a 35% decrease in morphine consumption in the lidocaine group for the first 72 hours, as well as higher pain scores in the placebo group. This morphine-sparing effect was more evident in the second half of the 72-hour period. When lidocaine is administered only during the postoperative period, there is no morphine-sparing effect.²⁸ Since opioid agents have been associated with postoperative ileus, morphine sparing contributes to a decrease in the duration of ileus.

In major orthopedic surgery, an analgesic benefit could be expected; however, since the incidence of ileus is low in that patient population, there may be fewer benefits from lidocaine compared with GI surgery. A recent study²⁹ revealed no pain reduction in patients undergoing hip surgery and receiving lidocaine; however, this lack of efficacy could be attributed to the relatively low pain scores reported, even in the control group.

Postoperative ileus and hospital stay

In colon surgery, postoperative ileus (POI) plays an important role after surgery, since it greatly determines the length of hospital stay and causes significant patient discomfort. POI is associated with postoperative pain, sympathetic hypertonicity, and blockade of parasympathetic pathways. Other factors may also contribute to this condition: postoperative use of opioid agents (dose-dependent effect), intraoperative hypothermia, and excessive intravenous saline intake.³⁰ Currently, shortening the duration of ileus is a primary key to early recovery following major GI surgery. Continuous intravenous lido-

caine after a loading dose is associated with a decrease in the duration of ileus, irrespective of the surgical technique.

Surgery by laparotomy

Herroeder et al⁷ examined the systemic effects of lidocaine on pain, ileus duration, and hospital length of stay after administration in patients undergoing open colorectal surgery who presented with contraindications to the insertion of a thoracic epidural catheter for postoperative analgesia. The authors of this prospective, double-blind study randomized 60 patients into 2 groups: lidocaine (1.5 mg/kg bolus at induction followed by a 2 mg/min continuous infusion continued up until 4 hours after closing of the abdominal wall) versus placebo. They found a significant difference ($P<0.004$) in the hospital length of stay: 7 days in the lidocaine group versus 8 days in the placebo group. In the lidocaine group, the time to first bowel sounds, first stools, and tolerance to solid food was significantly shortened; however, no difference was found in opioid consumption or pain scores.

Groudine et al⁵ demonstrated the advantage of a similar lidocaine protocol in radical retropubic prostatectomy. The randomized prospective study included 40 patients; 18 patients in the lidocaine group received a 1.5 mg/kg intravenous lidocaine bolus at the time of induction followed by a 2 or 3 mg/min continuous infusion (depending on weight) that was continued until 1 hour after skin closure. These patients were compared with a placebo group given a saline solution. Postoperative pain treatment consisted of systematic administration of ketorolac with morphine boluses, if needed. The results reveal an earlier reappearance of abdominal gases ($P<0.0073$), bowel movements ($P<0.02$), as well as a reduction in hospital length of stay ($P=0.043$) in the lidocaine group. There was also a 50% decrease in morphine requirements in the immediate postoperative period for the lidocaine group, but this benefit is not found beyond the recovery room. The use of a total pain score (the modalities of which are not revealed in the study) indicated pain reduction in the lidocaine group over the

entire hospital stay ($P<0.0001$). On the other hand, Rimback et al⁸ demonstrated several years earlier a faster transit of contrast medium after cholecystectomy in patients receiving intravenous lidocaine during the first 24 hours following the start of surgery.

Laparoscopic surgery

Over the past few years, laparoscopy has become increasingly popular in major GI surgery, because it leads to a reduction in postoperative pain, ileus duration, and hospital length of stay. Its benefits are such that the role of an epidural is currently questioned for this type of surgery.^{9,10} Kaba et al⁴ studied the advantages of systemic lidocaine administration in laparoscopic colon surgery to facilitate postoperative recovery. The study examined 40 patients (20 in each group) in a standardized anesthesia protocol with special attention to morphine sparing, early food intake, and early postoperative mobilization. One group of patients received a 1.5 mg/kg lidocaine bolus at the time of induction, followed by a 2 mg/kg/hr infusion during the first 24 hours postoperatively; the other group was given a saline solution. A reduction in sevoflurane requirements ($P<0.001$) to maintain stable hemodynamics during surgery was observed, as well as a decrease in opioid agents administered intraoperatively ($P<0.008$) in the lidocaine group. Morphine consumption during the first 24 hours postoperatively was less in the lidocaine group, and there was less pain during mobilization and less cough. Bowel sounds and stools reappeared earlier ($P<0.001$) in the lidocaine group and hospital stay was reduced by 1 day for these patients ($P<0.001$).

LIDOCAINE TOXICITY

Clinical symptoms compatible with toxic plasma levels of lidocaine were found in none of the clinical studies³⁻⁷ using 2 mg/kg/hr doses after a 1.5 mg/kg bolus. Measurement of plasma lidocaine concentrations performed during the various intraoperative and postoperative periods indicated lower local anesthetic concentrations than the toxic level of 5 $\mu\text{g/mL}$, despite prolonged infusions (Table 1).

TABLE 1: Lidocaine plasma concentrations after a protocol combining a bolus (b) and an infusion (i)

Studies	Lidocaine protocol	Infusion time	Plasma concentration
Koppert et al, 2004 ⁶ n = 20	b 1.5 mg/kg i 1.5 mg/kg/hr	6 ± 2 hours	1.9 ± 0.7 µg/mL*
Kaba et al, 2007 ⁴ n = 20	b 1.5 mg/kg i 2 mg/kg/hr	24 hours	1.6 ± 0.9 µg/mL at 5 min* 1.3 ± 0.4 µg/mL at 15 min* 1.8 ± 0.5 µg/mL at 60 min* 2.7 ± 1.1 µg/mL at 24 hr*
Groudine et al, 1998 ⁵ n = 20	b 1.5 mg/kg i 2 to 3 mg/min	NA	1.3-3.7 µg /mL**
Herroeder et al, 2007 ⁷ n = 33	b 1.5 mg/kg i 2 mg/min	NA	1.1-4.2 µg/mL**
Cassuto et al, 1985 ³ n = 10	b 100 mg i 2 mg/min	24 hours	1.52 ± 0.29 µg/mL at 8 hr* 1.75 ± 0.34 µg/mL at 20 hr*

* mean ± SD, ** confidence interval; NA = not available

KEY POINTS

- Lidocaine has anti-inflammatory, analgesic, antihyperalgesic and antithrombotic properties.
- In major GI surgery, lidocaine administered as an intravenous bolus at the beginning of surgery followed by a continuous infusion is associated with a decrease in morphine consumption, postoperative ileus duration, and hospital stay.
- Intravenous lidocaine is an interesting therapeutic option to improve postoperative recovery after abdominal surgery when epidural anesthesia is contraindicated or when its risk/benefit ratio is controversial, for instance in laparoscopic surgery.
- There is no systemic toxicity at 2 mg/kg/hr doses.

Dr. Série obtained his degree from the Faculty of Medicine of Université de Tours, France. He was an intern in anesthesia/resuscitation at the Hôpitaux de Tours. Currently, he is completing a fellowship at Hôpital Maisonneuve-Rosemont, a hospital centre affiliated with the Université de Montréal.

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ERRATA

In the last issue entitled “Airway Management in the Patient with Cervical Instability,” we identified two errors we wish to correct that eluded us during the editing process:

1) Page 4 featured the following paragraph:

“Recently, Turkstra et al²¹ compared the effect of DL, Trachlight[®] lighted intubating stylet, and GlideScope[®] videolaryngoscopy in normal subjects under general anesthesia with C-spine stabilization. While Trachlight[®] reduced the movement by almost one-half compared with DL, it offered no clinically significant reduction in movement. This finding was recently confirmed by Robitaille et al.²³”

This paragraph should have read:

“More recently, Turkstra et al²¹ compared the effect of DL, Trachlight[®] lighted intubating stylet and GlideScope[®] videolaryngoscopy in normal subjects under general anesthesia with C-spine stabilization. While movement with Trachlight[®] was nearly halved compared with DL, videolaryngoscopy offered no clinically significant reduction in movement, a finding that has been recently confirmed by another study.²³”

2) The Figures were wrongly attributed to White, AA III, Panjabi, MM. *Clinical Biomechanics of the Spine*. Philadelphia, PA: J.B. Lippincott; 1978. Their actual source is Crosby ET. Airway management in adults after cervical spine trauma. *Anesthesiology*. 2006;104: 1293-318.

We are sorry for these mistakes and for any inconvenience they might have caused.

The Editing Team

Dr. Série has no disclosures to announce in association with the contents of this issue.

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