Novel Approaches in Regional Anesthesia & Pain Management

Chapter 1

Novel Action of Local Anaesthetics (Literature Review)

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Abstract

The aim of this article is to review current data of Medline, PubMed and other databases on the effect of local anaesthetics (LAs) with respect to: mechanism of action, effect on postoperative and traumatic ileus, neuroprotection, prevention of cancer recurrence, immune system preserving effect (antiinflammatory and antimicrobial) and novel indications of LAs. Over the last decade scientific studies proved that LAs can interact with other receptors. Besides causing anaesthesia, the LAs may act directly on other receptors and their signaling pathways which are involved in processes of inflammation, platelet activation, nociception, peripheral pain and arrhythmias. Besides reduction in postoperative pain intensity at 6 and 12 h, perioperative use of systemic LAs for abdominal surgery is associated with reduction of opioid dose, length of hospital stay by 4 h, faster recovery of bowel function (peristalsis earlier by 8 h, first flatus by 14 h, less PONV). Several animal studies have proved neuroprotective effect of intravenous lidocaine. It reduces the level of glutamate in the hippocampus and cortex, attenuates apoptosis in the ischaemic area and reduces infarct size, thus improving recovery after hypothermic ischaemia. Long-term effect of anaesthesia/analgesia - reduction of cancer recurrence – was confirmed in several studies (breast, colonic, prostate). LAs reduce surgery-induced immune alterations by reducing production of both pro- and antinflammatory interleukines and also have antimicrobial properties and inhibit different m/o growth in vitro. In conclusion, besides analgesia and antiar-

rhythmia, local anaesthetics produce faster recovery of bowel function, mobility, reduced hospital stay, have neuroprotective and antimicrobial properties, reduction of inflammation and incidence of cancer recurrence. Further studies regarding safety and determination of optimal dosage are still needed.

Keywords: local anaesthetics; mechanism of action; postoperative ileus; neuroprotection; cancer recurrence.

Gudaityte J

1. Introduction

Local anaesthetics (LA) are widely used for regional anaesthesia and treatment of arrhythmias. The action mechanism of the LAs is connected to the reversible blockage of the Na+ channels dependent on voltage, impeding the influx of Na+ necessary to initiate and propagate the action potentials, maintaining the cell in a state of rest. Local anaesthetic acts by paralyzing the peripheral sensory nerve endings, or by interrupting the transmission of sensitivity to pain between the nerve endings (nociceptors) and the encephalon. These agents can also affect the potassium and calcium channels and act in intracellular space. Over the last decade scientific studies proved that LA can interact with other receptors. Besides causing anaesthesia, the LAs may act directly on other receptors and their signaling pathways which are involved in processes of inflammation, platelet activation, nociception, peripheral pain and arrhythmias. The aim of this article is to review current data on effect of LA with respect to: mechanism of action, effect on postoperative and traumatic ileus, neuroprotection, prevention of cancer recurrence, immune system preserving effect (antiinflammatory and antimicrobial).

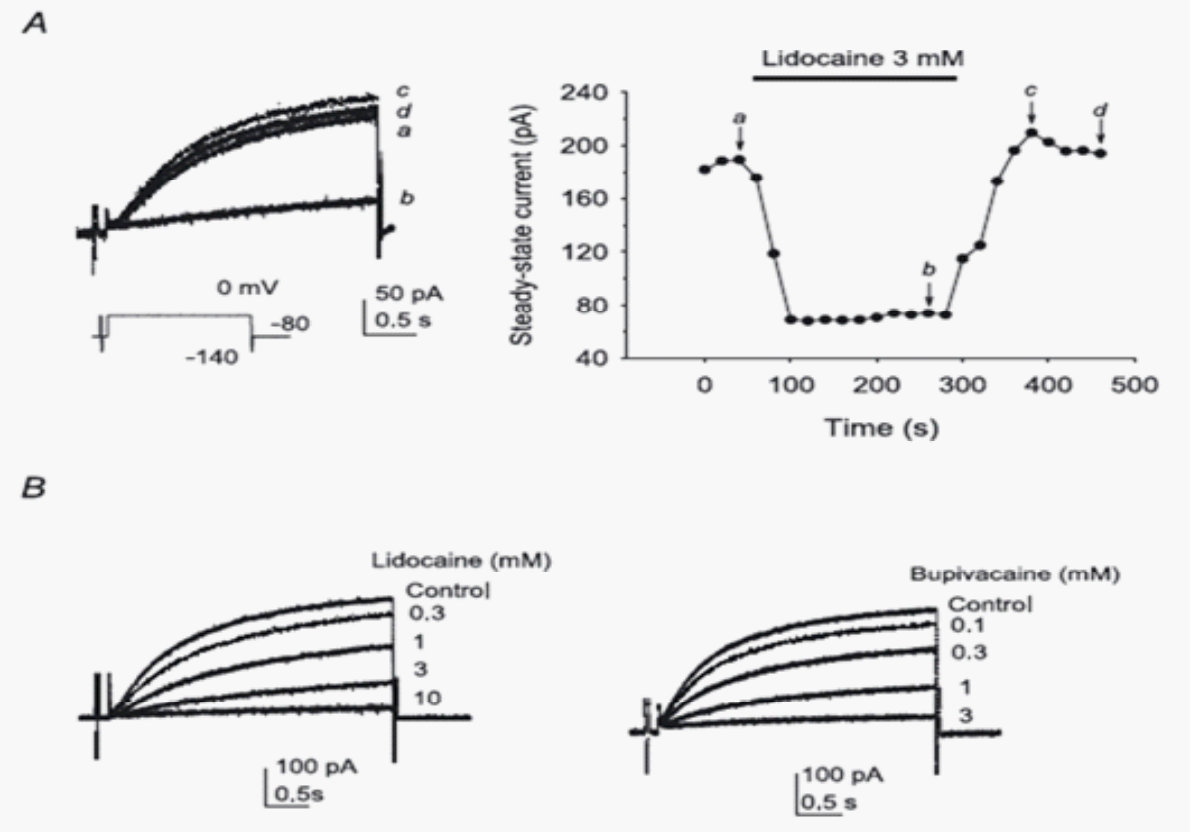
2. Review of LA's mechanism of action

2.1. Inhibition of voltage-gated proton channels

LAs are known to suppress phagocytosis and the production of reactive oxygen species in immune cells. Voltage-gated proton channels are abundantly expressed in immune cells, including microglia, and play crucial roles in sustaining phagocytosis. Matsuura T et al.'s study [1] revealed that both lidocaine and bupivacaine increase the intracellular p^H of microglia by their weak base properties and, consequently, inhibit proton channels. This is a novel mechanism of action. The picture below shows changes in the proton currents (left panel) and the time course (right panel) by perfusing the bath with the 3 mM lidocaine-containing solution. The ordinate indicates the steady-state current amplitudes fitted with a single-exponential function (0 mV, 3 s) applied at −80 mV. B, lidocaine (left) and bupivacaine (right) decreased the proton currents in a dose-dependent manner [Fig.1]. Matsuura T [1] et al. also presented another mechanism of action: inhibition of production of reactive oxygen species [Fig. 2]. Picture (A) shows time courses of ROS production measured by chemilluminescence in the absence and presence of lidocaine. Lidocaine suppressed the ROS production in a dose-dependent manner. (B) shows the peak values of chemilluminescence in the absence and presence of lidocaine or bupivacaine expressed as relative light units per second (RLU s−1) Data are mean ± SD (n = 5

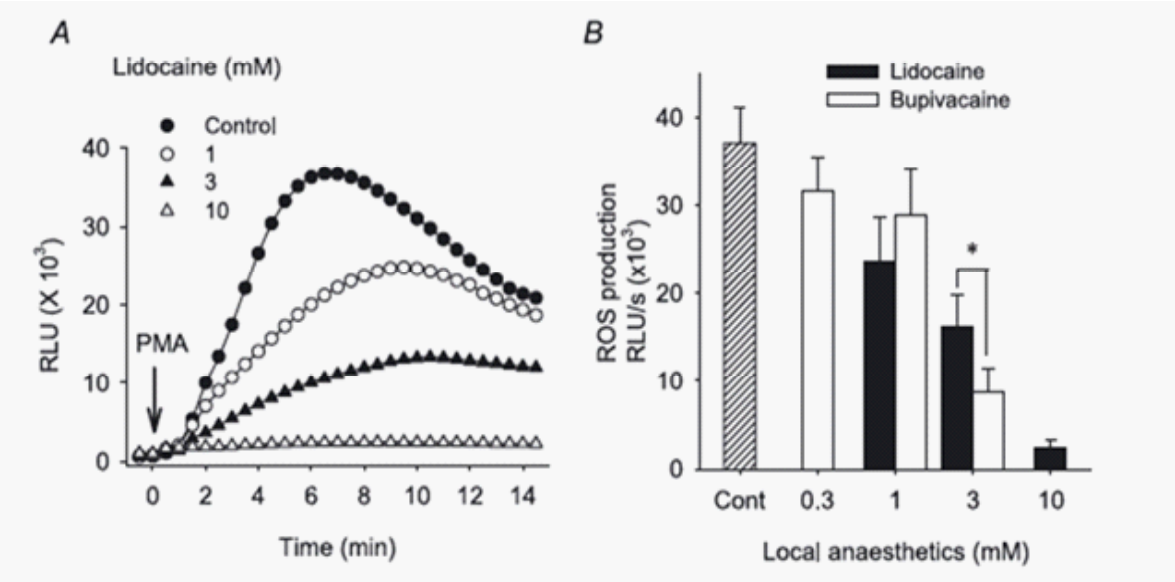
for each), *p< 0.05 lidocaine versus bupivacaine. LAs pathophysiologically act as a weak base and the inhibition is potentiated at low pHi (intracellular).

Figure 1. Lidocaine and bupivacaine proton channel inhibition of microglia [1].



A – changes in proton currents; B – lidocaine and bupivacaine decrease the proton currents [1]. Reproduced with permission of Wiley Global Permissions and MD PhD Takashi Mori.

Figure 2. Lidocaine and bupivacaine inhibition of production of reactive oxygen species [1].



A – lidocaine suppressed ROS production; B – peak values of chemilluminescence; means±SD; *p<0.05 lidocaine versus bupivacaine.

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2.2. Postoperative ileus (PI)

Postoperative ileus (PI) is a quite common complication of abdominal surgery. It is

well appreciated that epidural anaesthesia and analgesia can improve gastrointestinal function and reduce duration of PI. Scientific data suggest a possible positive effect of intravenous lidocaine. Lidocaine reduces hospital stay due to faster recovery of oral intake, improvement of peristalsis, reduction of nausea/vomiting, induction of faster defaecation and better postoperative analgesia. Dosage and duration of lidocaine treatment is different among studies: 1.5 mg/kg→ 2-3 mg/min (1 h after surgery) [2]; 1.5 mg/kg→ 2 mg/kg/h→ 1.33 mg/kg/h (24 h postoperatively) [3]; 1.5 mg/kg→ 2 mg/min (4 h after surgery) [4]; 1 mg/min (24 h postoperatively) [5]. In all these studies no toxic plasma level of lidocaine was found. Marret E et al. [6] presented a review article which revealed that continuous intravenous administration of lidocaine may decrease the duration of ileus. During this study three databases (Medline, Embase and the Cochrane Controlled Trials Register) were searched to include randomized controlled trials comparing continuous intravenous lidocaine infusion during and after abdominal surgery with placebo. Eight trials were selected. A total of 161 patients received intravenous lidocaine, with 159 controls. Intravenous lidocaine administration decreased the duration of ileus (weighted mean difference (WMD) − 8.36 h; $p < 0.001$). Continuous intravenous administration of lidocaine during and after abdominal surgery improves patient rehabilitation and shortens hospital stay. McCarthy GC et al. [7] performed a systematic review to determine the overall effectivenes of intravenous lidocaine infusion on recovery from surgery for patients undergoing various surgical procedures. Sixteen trials were included. A total of 395 patients received intravenous lidocaine versus 369 controls: first flatus occurred up to 23 hours earlier, while first bowel movement occurred up to 28 hours earlier in the lidocaine-treated patients. Patients receiving lidocaine infusion had faster return of bowel function and decreased length of hospital stay.

A systematic search by Vigneault L et al. [8] was performed using MEDLINE, EMBASE, Cochrane, and SCOPUS databases. The review included all randomized controlled trials that used a placebo or any comparator and evaluated intravenous lidocaine infusion (IVLI) during general anaesthesia for any type of surgery. From 5,472 citations retrieved, 29 studies involving a total of 1,754 patients were suitable. Perioperative intravenous lidocaine infusion reduced duration of postoperative ileus, length of hospital stay, and nausea/vomiting. Intravenous lidocaine infusion was effective mainly in populations of abdominal surgery.

Another type of PI that causes a lot of concern is due to severe spinal cord injury. Treatment with neostigmine is frequently ineffective. Baumann A et al. [9] presented a study in which i/v lidocaine infusion was administered for 7 patients after severe spinal cord injury (lidocaine bolus 1 mg/kg→ 2-3 mg/min). The results showed that gastrointestinal motility was restored in 5 patients after 10-20 h of treatment; lidocaine infusion for 36 h had no significant effect for 2 patients. This study also showed that i/v lidocaine reduces inflammatory reaction caused by peritoneal traction and/or attenuates posttraumatic and postsurgical stress. No side

effects were noticed. Despite the utility of lidocaine represented in all these studies there are still important questions to be solved – determination of the minimal effective dose of intravenous lidocaine and the duration of infusion.

2.3. Neuroprotection

Experimental data of animal studies revealed neuroprotective properties of LAs in models of transitory cerebral ischaemia. Neuroprotective effects of lidocaine in antiarrhythmic doses are as follows: reduction of glutamate storage in hippocampus and cerebral cortex [10], reduced ratio of ischaemic cortical, hippocampus and thalamic cells after retrograde cerebral perfusion [11] and improved functional neurological recovery and survival after hypothermal bloodflow reduction [12,13]. According to Wright JL et al. [14] the possible mechanism of neuroprotection in the early stage of hypoxia is increased level of intracellular Na+ which promotes rapid depolarization and neuronal damage. This Na^+ imbalance affects intracellular levels of Ca, ATP andexcitatory amino acids. Lidocaine may decrease ischaemic cell damage by: attenuation of ATP depletion, reduction of repetitive depolarization by Na influx blockade, scavenging free radicals, reduction of intracranial pressure and inhibition of glutamate. In 2009 Joseph PM [15] et al. introduced a randomized double – blinded placebo controlled study of neuroprotection with lidocaine in cardiac surgery in which 241 patient participated. The trial involved cardiac surgery with cardiopulmonary bypass. There were two groups of treatment: lidocaine group - bolus 1 mg/kg→ 1 mg/min 48 h and control group – 0.9% NaCl. The cognitive functions were assessed before surgery, at 6 weeks and 1 year postoperatively. The results showed that lidocaine did not decrease the risk of cognitive dysfunction. The total dose of lidocaine (≥35 mg/kg) affected cognitive functions for diabetic patients. Even more, the study presented a positive effect of low-dose lidocaine (≤42.6 mg/kg) on cognitive function for nondiabetic patients (n=166). In terms of cognitive function, lidocaine, especially in low doses, can be beneficial for a certain group of patients but not the total population.

2.4. Prevention of cancer recurrence

Surgery remains the cornerstone in cancer treatment. Surgery is associated with considerable neuroendocrine and metabolic response, and production of proinflammatory cytokines [16]. Thus transitory perioperative depression of immune function increases the risk of cancer recurrence [17]. Factors affecting cancer recurrence associated with surgery are migration of cancer cells into the circulation, depression of cellular immune response (T cells and NK function) and increased concentration of proangiogenetic factors. Cancer recurrence is assosiated with general anaesthesia which causes depression of immune function (neutrophils, macrophagues, T cells, NK function), opioids wich cause depression of cellular and humoral immune response; proangiogenesic effect [18]. Anaesthetic techniques such as paravertebral and epidural blockades with local anaesthetics for breast and prostatic cancer reduce the risk

of recurrence [17]. Regional anaesthesia and analgesia prevents cancer recurrence by reduction of neuroendocrine stress, requirements of general anaesthetics (and immune suppression) and requirements of opioids thus stimulating NK activity [18]. Recent in vitro studies revealed LAs have cytotoxic effects on neoplastic cells. An anti-proliferative effect on human tongue cancer cells, by inhibiting epidermal growth factor, was exhibited by lidocaine [19]. Lidocaine, bupivacaine, and ropivacaine reduced mesenchymal stem cell proliferation in vitro and transcription pathways related to initiation of neoplasia and metastasis were also inhibited [20]. LAs have also been reported to alter the DNA methylation status of certain cancer cell types and have been associated with the reactivation of tumour suppressor genes [21]. LAs have been associated with cytotoxic effects on T - lymphoma cells in vitro. Apoptosis was observed at lower concentrations, while necrosis was seen at higher concentrations. Eight LAs were studied in total and each exhibited varying cytotoxic effects, which appeared to correlate with their lipophilicity and potency [22]. A long-term follow-up analysis of the MASTER trial, a multicenter prospective clinical study in which patients undergoing major abdominal surgery were randomized to receive GA with either epidural or opioid analgesia found no difference in cancer-free survival between the groups. The median time to cancer recurrence or death was 2.6 yr in the epidural group, when compared with 2.8 yr in the opioid group. A potential confounding factor might have been the amount of volatile anaesthesia required intraoperatively, which was not recorded in the original MASTER trial. While the study was well powered to detect a one-third risk reduction, smaller but clinically significant effects might have been overlooked. Of note, older age, female gender, tumour node metastasis status, and allogenic red blood cell transfusion were all associated with reduced cancer-free survival [23].

2.5. Immune system preserving effect

Immune system preserving effect was shown in a randomized controlled trial led by Yardeni [24] in 2009 where 65 female patients who were scheduled for transabdominal hysterectomy, were randomized in to two groups (lidocaine and control group) and the effect of i/v lidocaine on postoperative pain and immune function was examined. Controlled epidural analgesia was performed to all patients. Pain intensity (VAS); blood samples (24, 48, 72 h after surgery) were examined to determine cytokine (IL-1ra, IL-6) production. Results showed that lidocaine group had lower VAS score 4 and 8 h after surgery and also reduced levels of IL-1ra and IL-6 in blood. IL-6 production increased during the postoperative period in the Sal PCEA group (n=28, $P<0.025$), whereas in the Lidoc PCEA group (n=29), the secretion of IL-6 did not change significantly. Sal PCEA patients (n=30) had increased IL-1ra production at 24 h ($P<0.0001$), 48 h ($P<0.0012$), and 72 h ($P<0.001$) compared with baseline ($P<0.01$). The production of IL-1ra in cells from patients in the Lidoc PCEA group (n=26) did not change significantly during the postoperative period. There was a significant increase in IL-1ra production at 24 h only in the Sal PCEA group versus Lidoc PCEA group ($P<0.02$). Perioperative i/v

lidocaine improves immediate postoperative pain management and reduces surgery-induced immune alterations by reducing production of both pro- and antinflammatory interleukines [24].

2.6. Antiinflammatory effect

Inflammation is a complicated reaction to harmful agents with tissue and blood vessels, functional and structural changes. When inflammation occurs signs of erythema, oedema, elevated temperature, pain, organ dysfunction develop. LAs cause reversible inhibition in the inflammatory cascade for leucocyte adhaesion to endothelium, leucocyte migration through the vessel wall, activation of neutrophils, phagocytosis of granulocytes and synthesis and secretion of certain inflammatory mediators (PG, histamine, TX, LT, O_2 free radicals, cytokines) [25]. LAs have no effect on activation of polymorphonuclear leucocytes (PMNL), but selectively reduce the „priming“ process. This process is associated with PMNL potentiated response to subsequent activating stimulus [14]. This differs LAs from other antiinflammatory drugs such as steroids. There is no scientific evidence that LAs increase the risk of infection or mortality from sepsis or suppress wound healing [16]. Caracasa [26] et al. investigated therapeutical use of lidocaine as an anti-inflammatory substance. A search on health sciences databases was performed which reported in vivo experimental studies that tested lidocaine as an anti-inflammatory substance and used morphological and/or biochemical analysis. Only 10 articles met the inclusion criteria. Despite methodological differences, all of them, except for one, reported that lidocaine showed anti-inflammatory effects.

2.7. Antimicrobial effect of LAs

LAs have antimicrobial properties and inhibit different m/o growth in vitro. Parr AM et al. [27] conducted a study which revealed that lidocaine has got dose dependant antimicrobial properties. Supreme sensitivity for lidocaine had gram-negative bacteria (*E.faecalis, E.coli*), and the least sensitive was *S.aureus*. Epinephrine used as a supplement had no significant influence. Stratford AF [28] et al.'s works with pigs showed that infiltration of surgical wounds with 2% lidocaine before live *S.aureus* inoculation, was associated with decreased growth in bacterial colonies by 70 %. The precise mechanism is not known. There are several possible mechanisms. One of them involves reduction of bacterial membrane predecessors, the other claims that LA inhibits bacterial membrane permeability and has impact on cellular metabolism.

Epidural abscess is one of most serious complication of epidural anesthesia. Coghlan MW et al. [29] conducted a trial of different LAs and supplements for epidural infusions and examined their antimicrobial properties. Minimum inhibitory concentrations of different epidural agents are shown in the table (Table). Bupivacaine has got the highest antimicrobial properties: 0.125 – 0.25 % solution had antimicrobial properties for *S.aureus, E.faecalis*,

E.coli; *P.aeruginosa* was not affected. Levobupivacaine and ropivacaine had no significant effect on examined bacteria. Additives such as fentanyl, epinephrine, clonidine, also had no impact on antimicrobial activity [29].

3. Conclusion

LAs are chemical compounds with multiple effects. Scientific research over the last decade revealed that inhibition of sodium channels is not the only one mechanism of action of these drugs. LAs reduce postoperative and traumatic PI through improved peristalsis and faster defaecation, reduced nausea/vomiting and reduced inflammatory reaction caused by peritoneal traction and/or attenuates posttraumatic and postsurgical stress. Experimental studies have shown that LA's decrease ischaemic cell damage and prevent cancer recurrence by reduction of neuroendocrine stress and stimulation of NK activity. LAs cause reversible inhibition in the inflammatory cascade and have antimicrobial properties and inhibit different m/o growth *in vitro*. There is growing evidence that LAs have a broad spectrum of indications, but further, large-scale randomized controlled trials and multidisciplinary approach are needed to confirm clinical effect of laboratory studies. At present, there is still insufficient evidence to make changes in clinical practice.

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