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Chapter 5

A Review of Intravenous Lidocaine Infusion Therapy for Paediatric Acute and Chronic Pain Management

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Additional information is available at the end of the chapter

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To raise new questions, new possibilities, to regard old problems from a new angle, requires creative imagination and marks real advance in science.

Albert Einstein [1]

Abstract

Pediatric acute and chronic pain experiences involve the interaction of physiological, psychological, behavioural, developmental, pharmacological and situational factors. In the acute perioperative pain setting preventative multimodal analgesia is required to provide comfort and minimise the potential for "wind-up" and central sensitisation. When pain is recurrent, ongoing or chronic some children embark on a downward spiral of decreased physical, psychological and social functioning. The multidisciplinary team management approach is a well-established standard of care for children with complex chronic pain. Intravenous lidocaine has peripheral and central mediated analgesic, anti-inflammatory and anti-hyperalgesic properties. Intravenous lidocaine infusion therapy (IVLT) has been shown to be effective in the management of acute and chronic pain in adults. This chapter will present the rational for IVLT in pediatric pain management with emphasis on preventative multimodal therapy in acute pain and the multidisciplinary treatment approach in chronic pain. Large multi-centre randomised controlled trials are required to provide the evidence-base to confirm that IVLT is indeed an effective and safe treatment option in acute preventative multimodal analgesia and as an adjunct in the multidisciplinary care of chronic pain in the pediatric population.

Keywords: lidocaine, acute pain management, chronic pain management, paediatric

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1. Introduction

1.1. Paediatric pain

Pain is described as an unpleasant sensory and emotional sensation associated with actual or potential tissue damage [2]. Pain is a normal physiological response to injury that protects an injured area at the time of healing. The experience of pain is the consequence of neuro-inflammatory activity and its interaction with complex peripheral and central nervous information-processing networks. It is not a simple hardwired impulse to sense message. The complex sequence of electrochemical events that take place from the site of injury to perception of pain is known as nociception. External noxious energy from the site of injury is converted into electrophysiological activity (transduction). This coded information is relayed via multiple parallel ascending pathways through the spinal cord to the brainstem, thalamus and sensory cortex (transmission). Incoming nociceptive traffic can be modified at any point in this transmission pathway by descending inhibitory pathways (modulation) [3]. The periaqueductal grey region, within the midbrain, and the periventricular grey matter connect anatomically with the rostroventral medulla and send descending excitatory projections to the dorsal horn of the spinal cord. Finally, connections between the thalamus and other higher cortical centres integrate the autonomic, affective and emotional responses to give a cumulative perception of pain [4]. It is important to note that pain pathways show remarkable neuroplasticity, changing phenotype in response to sustained inputs [5].

The paediatric experience of pain is influenced by many factors including the degree of tissue damage, age, sex, pharmacogenetic profile, previous pain experiences, cognitive factors, emotional issues, behavioural aspects, family background, environment, peer groups and culture. Due to the diverse interplay of these factors, there is substantial inter-individual variability in pain perception for different child/youths who have undergone the same surgical insult. In addition inter-individual variability in response to medications due to pharmacogenetic, sex, cultural, cognitive and emotional factors means that the analgesic response to doses of analgesia medication is also not predictable. Hence, the nature of pain as a sensation and its overall significance to a child/youth is unique. The resulting uncertainty in an individual child's pain perception and response to medications dictate that pain therapy is targeted according to ongoing individual assessment and response. Safe clinical practice requires appropriate understanding of pain pathophysiology, different pain models, pain assessment in different aged children and the age-related changes in the pharmacokinetics and pharmacodynamics of analgesics in infants and children. In an effort to comprehend why IVLT is effective, it is essential to understand some the mechanisms integral to pain physiology and pathophysiology.

1.2. Pain physiology and pathophysiology

Nociceptors are the free nerve endings of primary afferent pain nerve fibres responsible for the detection of noxious (unpleasant) stimuli, transforming the stimuli into electrical signals that are conducted to the central nervous system. Nocioceptors are distributed throughout the body and can be stimulated by mechanical, thermal or chemical stimuli.

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Tissue injury induces an inflammatory reaction with an increase in acute phase proteins and the release of vasoactive mediators from mast cells and platelets. This inflammatory reaction includes activation of the kinin, complement and cytokine systems with release of inflammatory markers such as endothelin, prostaglandin E2, leukotrienes, substance P, bradykinin, cytokines, serotonin and adrenaline. These inflammatory markers induce peripheral nocioceptor sensitization and increased neuronal excitability [6–8]. These changes are partly caused by a change in levels of growth factors such as nerve growth factor, brain-derived neurotrophic factor, neuotrophin-3 and glial-cell derived neurotrophic factor [5].

Activation of nocioceptors creates energy that is converted into electrophysiological activity and transduced. Action potentials are created by activity of voltage-gated sodium and potassium channels which then propagate through axons to synapse in the dorsal horn [9]. The spinal-dorsal horn receives this nocioceptive information principally from primary afferent A-delta and C fibres. A-delta fibres are medium diameter myelinated axons that transmit acute afferent, localized sharp pain sensation. C fibres are small diameter un-myelinated afferents and convey delayed poorly localized pain. In the dorsal horn depolarization opens voltage-gated calcium channels (VGCC) which release substance P and glutamate that activate second-order neurons.

Following injury, the inflammatory mediators released also activate G-protein-coupled receptors expressed on sensory neurons. These are of fundamental importance for intra- and inter-cellular communication pathways [10] and play an important role in pain modulation and inflammation [11, 12]. It is relevant to note that cell membranes of injured peripheral nerves can exhibit an increased density in sodium channels and produce ectopic impulse generation and persistent spontaneous discharge in these nerves, their dorsal root ganglia, as well as neighbouring un-injured neurons [13–20]. As these spontaneous discharges have been shown to develop in both myelinated and un-myelinated nerve fibres, it is evident that ectopic activity can arise in both nociceptors and low-threshold mechanoreceptors [21]. Voltage-gated sodium channels (VGSC) with distinct gating and pharmacological properties have been reported to be upregulated in adult neurons by injury or disease [22]. An increased expression of sodium channels in dorsal root ganglia and around the injury site of injured axons contributes to spontaneous firing of nerve fibres after injury [23]. Changes in expression of sodium channels also occur in chronic neuropathic and inflammatory pain states [20, 24–28]. Changes in the properties and expression of voltage-gated calcium channels are also observed in neuropathic pain [29].

The non-selective cation channels, which make up the transient receptor potential (TRP) family of ion channels, are also key components in nocioception [30–32] and neurogenic inflammation [33, 34]. The transient receptor potential vanilloid 1 (TRPV1) and ankyrin 1 (TRPA1) channels are members of this TRP family. TRPV1 and TRPA1 are expressed on some sensory nerves and dorsal root ganglia [35]. They inter-link considerably with each other in terms of function, except, only TRPV1 is activated by vanilloids, like capsaicin (the piquant component of chili peppers). About 97% of TRPA1-expressing sensory neurons express TRPV1, while 30% of TRPV1-expressing neurons express TRPA1 [36]. TRPA1 is a molecular sensor of potentially toxic chemicals [37, 38] and is also activated by low temperatures [38, 39], mechanical stimuli [40, 41], and elevation of intra-cellular Ca^{2+} [42]. TRPA1 is, therefore, involved in the generation of pain signals associated with exposure to noxious chemicals, cold and mechanical stimuli [31].

In animal models of inflammatory and neuropathic pain, TRPA1 is up-regulated in sensory neurons [43, 44] and TRPA1 antagonists have been found to exhibit analgesic properties [45–47].

The terminals of C and A-delta fibres are concentrated in the superficial dorsal horn, C and Ad fibres terminate in lamina I (marginal zone) and lamina II (substantia gelatinosa) with some Ad fibres also terminating in lamina V. These fibres activate second-order neurons as well as modulatory inter-neurons (located in laminae V and VI). Primary afferent terminals release a number of excitatory neurotransmitters including glutamate and substance P.

Primary afferent nociceptive inputs synapse in the dorsal horn utilizing alpha-amino-3-hydroxy-5-methyl-4-iso-xazolepropionate (AMPA), neurokinin-1, and calcitonin gene-related peptide. Glutamate has a fundamental role in the activation of both AMPA and N-methyl-D-aspartate (NMDA) receptors in the dorsal horn, which generate excitatory post-synaptic potentials. Substance P belongs to the neurokinin group of small peptides, its effects are mediated by its binding to the NK1 receptor. The substance P-NK1 (SP-NK1) receptor system is present in only a minority of neurons (5–7%) and only in certain areas of the central nervous system. Release of substance P is induced by injurious stimuli, and the extent of its release is proportional to the strength and frequency of stimulation.

Glycine also serves an important role in central neurotransmission. It is an inhibitory neurotransmitter, and a co-agonist with glutamate at the NMDA receptor. These actions depend on extracellular glycine levels, which are regulated by glycine transporters. Ablation or silencing of spinal glycinergic neurons induces hyperalgesia and spontaneous pain behaviours, while their activation evokes analgesia against acute and chronic pain in rodents [48]. During high neuronal activity, glycine released from inhibitory inter-neurons escapes from the synaptic cleft, reaches nearby NMDA receptors and stimulates the NMDA receptor.

It is important to realize that different pain states (i.e. neuropathic/cancer/inflammatory) do create a unique but different set of neurochemical changes within sensory neurons, dorsal root ganglia and the spinal cord [5, 49].

Information from second-order neurons is relayed via the spinal cord to the brainstem and thalamus. Connections between the thalamus and higher cortical centres integrate the affective and autonomic responses to pain perception. In addition, descending axons from the brainstem synapse and release serotonin, noradrenaline and enkephalins in dorsal horn to also modify nociceptive transmission.

Primary afferent A-beta fibres are large-diameter myelinated nerves, which transmit mechanical information such as light touch. A-beta fibres do not usually activate nociceptive neurons and therefore do not transmit pain. The terminals of A-beta fibres are concentrated in the deeper dorsal horn and mainly target excitatory and inhibitory inter-neurons. However, the dorsal horn neuronal interconnections are modified and modulated under pathological conditions, such as peripheral nerve injury or peripheral tissue inflammation from injury or surgery [50–52]. Peripheral injuries may trigger on-going increases in the excitability of neurons (sensitization). This occurs at the level of the primary afferent nociceptive peripheral neuron (peripheral sensitization) and at the dorsal horn of the spinal cord (central sensitization).

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Reduction in the threshold for activation of nociceptive neurons is manifest as allodynia (a non-painful stimulus perceived as painful) and hyperalgesia (a mild painful stimulus perceived as severe or long-lasting pain). Allodynia or touch-evoked pain is A-beta mediated [53].

Complex interactions occur in the dorsal horn between afferent neurons, inter-neurons and descending modulatory pathways (see below). These interactions determine activity of the secondary afferent neurons. Glycine and gamma-aminobutyric acid (GABA) are important neurotransmitters acting at inhibitory inter-neurons.

Neuropathic pain may involve anomalous excitability in the dorsal horn, resulting from multiple functional alterations including; loss of function of inhibitory inter-neurons, reduced effectiveness of the inhibitory neurotransmitters, sprouting of wide dynamic neurons and activation of microglia, the immune cells of the CNS [54–56]. Microglia activate, respond and transform to reactive states through hypertrophy and proliferation [57, 58]. These activated microglia induce/enhance production and release of pro-inflammatory cytokines and brain-derived neurotrophic factor [59], which modulate the activity of dorsal-horn neurons [60].

"Wind up" is physiological activation in the spinal cord after an intense or persistent barrage of afferent nociceptive impulses [57, 61]. Central sensitization refers to enhanced excitability of dorsal-horn neurons and is characterized by increased spontaneous activity, enlarged receptive field areas, and an increase in responses evoked by large and small calibre primary afferent fibres. IASP taxonomy defines central sensitization as increased responsiveness of nociceptive neurons in the central nervous system to their normal or sub-threshold afferent input [2]. Secondary hyperalgesia (hyperalgesia in undamaged tissue adjacent to the area of actual tissue damage) is due to an increased receptive field and reduced threshold of wide dynamic neurons in the dorsal horn.

Central sensitization and wind-up intensify pain perception, and both depend on activation of N-methyl-ᴅ-aspartate (NMDA) receptors. Pain memories imprinted within the central nervous system by NMDA-receptor activation produce hyperalgesia and allodynia. NMDA glutaminergic synapses do not participate significantly in primary nociceptive transmission, but instead in spinal sensitization. NMDA blockade in the spinal cord does not prevent primary afferent transmission of nociceptive information to the thalamus. Therefore, any attempt to reduce pain needs to target nociception, as well as wind up and central sensitization.

The increased barrage of pain impulses secondary to peripheral and central sensitization confers change within the nervous system known as neuroplasticity. That is, the nervous system undergoes maladaptive changes in response to incoming pain signals by reorganizing its structure, function and connections. Patients with ongoing or chronic pain demonstrate such structural brain changes as well as abnormal functioning of the inhibitory pain-modulatory system [62]. In addition, in chronic-pain conditions, the primary brain areas accessed through classical acute pain pathways decrease in their activation incidence and pre-frontal cortex activity increases [63]. A simplified depiction of acute and chronic pain pathways is depicted in **Figures 1** and **2**.

For more detailed information, please review "The Basic Science of Pain" by Philip Peng (https://itunes.apple.com/ca/book/the-basic-science-of-pain/id1174147456?mt=11).

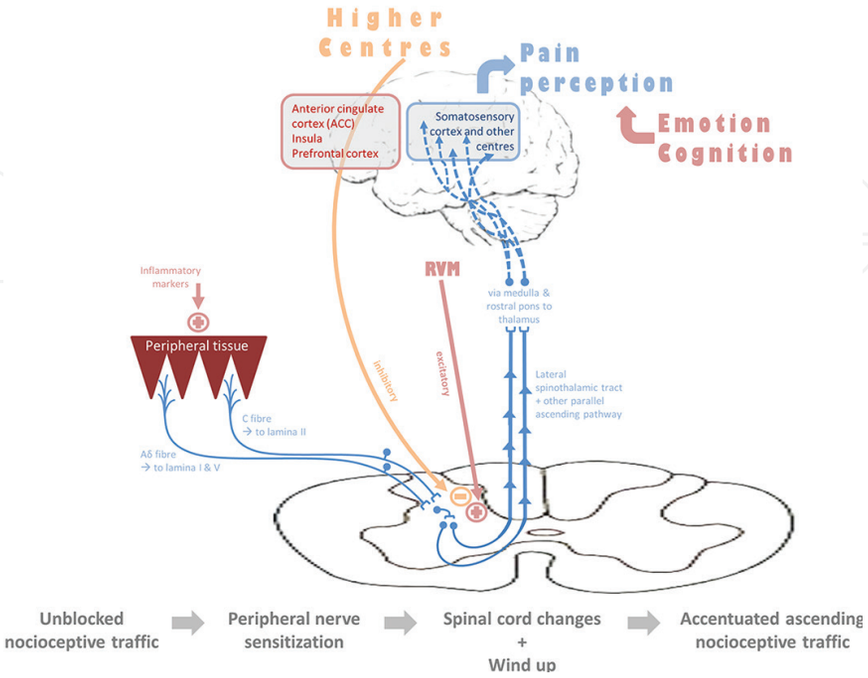


Figure 1. Simplified acute pain pathways.

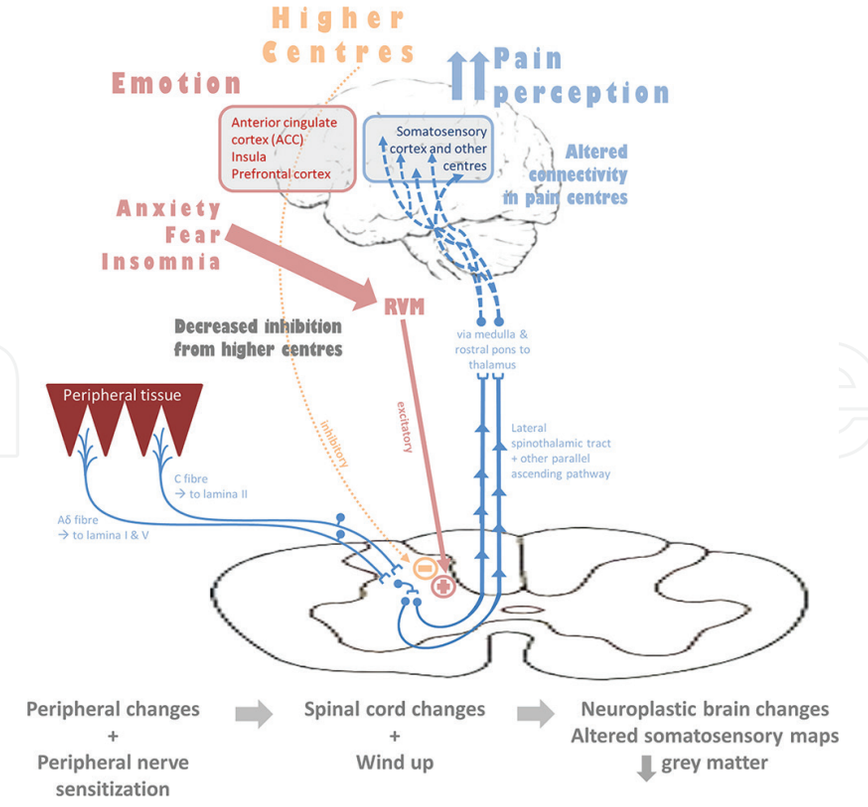


Figure 2. Simplified chronic pain pathophysiology.

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1.3. Impacts of poorly managed acute pain

When acute pain is not well-managed, deleterious effects on physiology, functional recovery and psychology can develop. Changes include increased morbidity such as nausea, emesis, poor oral fluid intake, sleep disturbance and behavioural changes. Ongoing discomfort and distress have a negative impact on child and family satisfaction and may be associated with poor recovery, anxiety, fear and reduced quality of life measures [64–71].

Physical and psychological responses to pain not only affect children's health directly but may also predispose them to develop chronic post-surgical pain (CPSP). Chronic pain affects approximately 20% of the adult population of which 22.5% develop their condition after surgery [72]. CPSP occurs following 10–50% of adult operations in which 2–10% of these adult patients will experience severe chronic pain [73]. The incidence of CPSP in the adult population is found to depend on a number of perioperative factors, which include genetic predisposition, younger age, degree of pre-operative anxiety, degree of catastrophization, depression, pre-operative pain status, the surgical pain model, surgical technique, length of surgery and the quality of acute post-operative pain management [73–76]. CPSP will often be neuropathic, resulting from nerve damage during surgery. CPSP studies in children are limited with a preliminary incidence of CPSP reported as 13–25% [77–80]. Prospective studies after spine surgery have also demonstrated prevalence rates of CPSP between 11 and 22% with risk factor for development of CPSP including high levels baseline pain intensity, anxiety and older age [81–83]. Recently, Rabbitts et al. found two distinct pain trajectories following major surgery in children; most children follow a positive early recovery pathway, whereas 22% follow a late recovery trajectory. One of the factors of the late recovery group was the presence of baseline parental catastrophizing (not child/youth catastrophizing) [84]. Nikolajsen and Brix also identified factors for risk of CPSP in children as older age, pre-op pain, acute postoperative pain and psychological factors, especially anxiety [85]. Some of these children/youth will go on to develop chronic pain in adulthood [86]. All these complications of poorly managed acute pain ultimately increase healthcare utilization and have an economic cost for both families and the health-care service. It is, therefore, essential to minimize post-surgical pain to prevent pain-related complications. This may be achievable with the adoption of preventative multimodal analgesia to minimize nociceptive traffic and reduce wind up and central sensitisation.

1.4. Preventative multimodal analgesia

Preventative analgesia is defined as analgesia that is provided by an intervention given in the perioperative period, which may be before or after incision and surgery, that reduces analgesic requirements for post-operative pain for a period longer than the duration of action for the analgesic intervention. Consideration needs to be given, not only to efficacy of analgesia regimens, but also that the duration pain management so that it spans the whole painful experience from incision to healing [87, 88]. Preventative analgesia differs from pre-emptive analgesia, where an analgesic intervention is administered pre-operatively with the aim to provide improved analgesia post-operatively compared with the identical analgesic intervention administered after incision or in the post-operative period [89].

Multimodal analgesia utilises combinations of analgesics that act by different modes to enable a reduction in analgesic requirements of each type of medication and therefore reduce side-effect profiles. The components of multimodal analgesia are shown in **Table 1**. A multimodal approach provides significant benefits, which include reduction in; pain intensity, opioid dose requirements, and opioid-related adverse events [68, 90–93]. In the acute perioperative pain setting, preventative multimodal analgesia is required not only to provide comfort but also to minimise the potential for "wind-up" and central sensitisation. Therefore, directly impacting, the mechanisms may induce the development of CPSP or chronic pain [94].

Acetaminophen
NSAID's including COX-2 inhibitors
Local anaesthetic agents
Opioids
Anxiolytics
Adjuvant medications: ketamine, clonidine, dexmedetomidine, pregabalin/gabapentin
Non-pharmacological techniques:
Education
Hypnosis
Cognitive behavioural therapy; relaxation/imagery/controlled breathing
TENS
Acupuncture
Massage
Distraction techniques (games/videos/virtual reality/computer games)

Table 1. Multimodal analgesia comprises a combination of the following modalities.

Although multimodal analgesia has been shown to be effective in reducing pain in children [95, 96], it should be remembered that many drugs used worldwide for paediatric pain management do not have approved labelling for use in children [97]. Drug dosing recommendations based on clinical evidence and experience, not based on evidence may well put children/youth at risk for medication-related adverse events [98].

A limited number of well-conducted, prospective randomized controlled trials have demonstrated improved clinical outcomes with respect to analgesia and opioid-related side effects with multimodal (vs. single) therapy [92, 93, 99]. However, there is an urgent need for research evaluating, which preventive multimodal analgesic regimens are most effective for different paediatric acute pain settings or surgical models of pain, the most appropriate timing of administration and which of these decrease or prevent long-term pain after surgery. In the meantime, paediatric acute pain teams need to develop surgery specific multimodal analgesia guidelines [100], assess effectiveness and respond quickly when the regime proves inadequate for an individual child/youth.

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Good quality acute pain management enhances functional recovery, improves long-term functional outcomes [101] and improves patient and family satisfaction [93, 102].

Non-pharmacological techniques are an extremely useful component of multimodal therapy [103–105]; unfortunately, they are under-utilised in hospitalised children [106]. The mainstay of acute pain management for children and youths resides in the use of opioid analgesia, but opioid use is associated with a significant side effect profile (see **Table 2**). Adverse effects (except allergy) are dose-related and may be relieved by minimizing the opioid dose, conversion to a different opioid and/or using non-opioid adjuvants. IVLT is a useful adjuvant for specific acute pain procedures.

Sedation
Respiratory depression
Nausea and vomiting
Pruritus
Meiosis
Urinary retention
Ileus/constipation
Myoclonic jerks
Dysphoria/hallucinations
Opioid-induced hyperalgesia [107]
Long term opioids in mice cause dose-dependent enhanced sarcoma-induced bone loss, fracture and bone pain [108]
Decreased regional grey matter volume [109]
Inhibit cellular and humoral immune function in humans [110]
Tolerance: physiologic adaptation that results in a decreased medication effect at its current dose or when needing a higher dose to maintain the desired analgesic effect [65]
Dependence: physiologic effect of opioid use resulting in withdrawal symptoms following abrupt discontinuation of opioids or after administration of opioid antagonist [65]
Long term potential for addiction (unlikely in pediatric, short-term, acute postoperative opioid therapy)
Long term endocrine effects [111]
Potential for diversion and abuse of prescription opioids in community [112]

Table 2. Adverse effects of opioids.

2. Intravenous lidocaine therapy

2.1. Lidocaine pharmacology

Local anaesthetics are primarily used for local infiltration, nerve blocks and regional anaesthesia. Analgesia results from blockade of voltage-gated Na^+ channels that prevent action potential initiation and propagation. Local anaesthetics impede sodium ion access to the axon interior, probably by physically occluding the trans-membrane sodium chan-

nels. This is a reversible process, which does not damage the nerve. Depolarization cannot take place when the sodium channel is blocked, so the axon remains polarized. A local anaesthetic regional or nerve block is, therefore, a reversible, non-depolarization block. In contrast, systemically administered local anaesthetics produce analgesia at plasma levels well below that required to block an action potential. Systemic administration of local anaesthetic is most recognized with lidocaine due to its widespread use for anti-arrhythmic treatment [113–115].

Lidocaine is an amide local anaesthetic and a Class Ib cardiac anti-dysrhythmic agent [116]. Therapeutic plasma levels and duration of IVLT for acute pain management are not well defined, although the optimal therapeutic range for acute pain treatment appears to be between 1 and 5 μg/ml [6, 24, 117–120]. Only preservative free formulations should be given intravenously. Bolus administration of 2 mg/kg and a continuous infusion of 2–5 mg/kg/h have shown to reach plasma levels of 1–4 μg/ml [121]. After a bolus injection or continuous administration for up to 12 h, the half-life of lidocaine is about 100 minutes and shows linear pharmacokinetics [122].

Lidocaine metabolism occurs rapidly in the liver by cytochrome P450 isoforms CYP1A2 and 3A4, as outlined in **Figure 3**. Lidocaine undergoes oxidative N-dealkylation, to a number of metabolites that include monoethylglycinexylidide (MEGX) and glycinexylidide (GX), and N-ethylglycine (NEG), all of which have a glycine-like moiety. Less than 10% of lidocaine is excreted unchanged by the kidneys. MEGX is an active metabolite and has 80% potency of lidocaine at VGSC's. GX is also active but NEG is inactive. Following intravenous administration, MEGX concentrations in serum range from 11 to 36% of the lidocaine concentration. All lidocaine metabolites are excreted by the kidneys. The half-life of lidocaine elimination from the plasma following IV administration is 81–149 min (mean 107 ± 22 SD, n = 15). The systemic clearance is 0.33–0.90 l/min (mean 0.64 ± 0.18 SD, n = 15). Children older than 6–7 months of age distribute and eliminate intravenous lidocaine in the same manner as adults [123].

In infants less than 6–7 months of age liver metabolism is immature so metabolism of drugs is delayed, and plasma protein levels are lower [124]. There are low levels of plasma alpha-1-acid glycoprotein, which increases the free fraction of circulating lidocaine and therefore increases the risk of toxicity [125]. IVLT in high doses (6–8mg/kg/h without a bolus dose) has used to treat neonatal seizures but the risk-benefit indication is considerably different than for pain management [126]. For these reasons, IVLT for pain management cannot be recommended in infants until more evidence of efficacy and safety in this population are available.

2.2. Safety of IVLT for pain management

A major advantage with IVLT is that appropriate use in adults is not associated with a significant side-effect profile [7, 127, 128]. In adults, a 100 mg bolus followed by an infusion at 1 mg/min, which approximates to 1mg/kg/h, produces a plasma level of just over 1 μg/ml in normal individuals with no co-morbidities [129]. IVLT doses used to manage pain are usually in the range of 1–2 mg/kg/h. Plasma levels at this rate of infusion are generally less than 3–5 μg/ml, but awake patients may complain of light-headedness, perioral numbness, dizziness and or

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sedation. Toxic plasma lidocaine levels are considered to be in the >6 μg/ml range [130]. Early signs of local anaesthetic systemic toxicity (LAST) will present as perioral numbness, metallic taste, tinnitus, visual and auditory disturbances, paresthesias, nausea, dizziness and drowsiness [7, 131–133]. Due to the short half-life of lidocaine, the symptoms of LAST are easily reversible by lowering or discontinuing the infusion. To provide some perspective, lidocaine effects at higher plasma levels are more serious; at 8 μg/ml, patients experience visual or auditory disturbances, dissociation, muscle twitching, and decreased blood pressure. At 12 μg/ml, convulsions can occur; at 16 μg/ml, coma may develop, and at levels above 20 μg/ml respiratory arrest and cardiovascular collapse ensue [132]. Physicians administering IVLT must be aware of algorithms of care to prevent, recognise and treat LAST when it occurs [134].

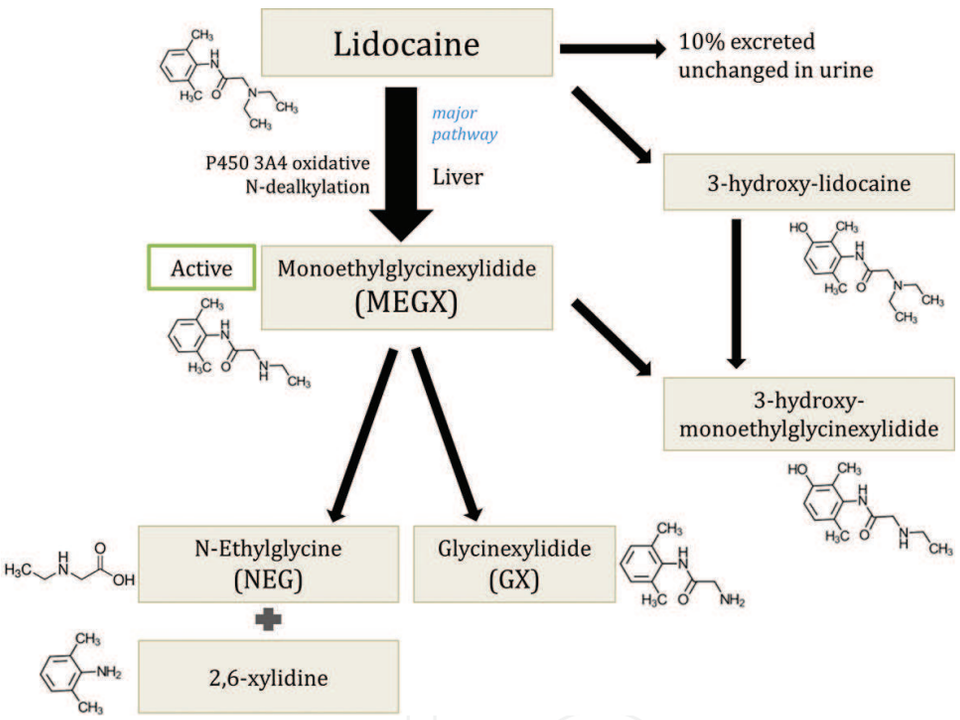


Figure 3. Lidocaine metabolism.

Contraindications to IVLT include allergy to amide local anaesthetics, significant cardiac disease, heart block, seizures, liver disease and/or significant renal impairment.

2.3. The rationale for IVLT in the management of pain

Studies in animal preparations clearly indicate that systemically administered lidocaine can silence ectopic discharges without blocking nerve conduction [135, 136]. Systemic administration of local anaesthetics provides clinical analgesia in a broad range of neuropathic pain states [23, 117, 137–140]. IVLT induces global analgesia and dampens the neuro-inflammatory response in pain [126, 141–144]. Lidocaine exerts its different effects on the neuro-inflammatory response by inhibiting ion channels and receptors. The exact lidocaine plasma level and duration of infusion

required to produce this effect are unknown; however, it occurs at levels below those required for action potential initiation and propagation for neural blockade. It is also not known if plasma lidocaine concentration correlates with analgesic effect in a dose dependent manner as different channels and receptors are modulated at different plasma lidocaine concentrations [145].

Intravenous lidocaine has peripherally and centrally mediated analgesic, anti-inflammatory and anti-hyperalgesic properties. Its analgesic properties reflect the variable dose, time dependent, multimodal aspect of its action on voltage-gated channels receptors and neurotransmitters that affect nociceptive transmission pathways [24, 45, 146–148]. In vitro, low dose lidocaine inhibits voltage-gated sodium channels (VGSC), some potassium channels, the glycinergic system, and G-protein coupled receptors. Higher dose lidocaine blocks voltage-gated calcium channels, other potassium channels, and NMDA receptors [145, 149, 150]. Lidocaine dosages needed for voltage-gated sodium channel blockade range from 60 to 200 μM, whereas voltage-gated calcium channel blockade occurs at higher doses in the 1–10 mM range [6, 151–153]. A number of different sodium channel isoforms exist with distinct tissue distribution and possibly distinct physiological functions. Some of these isoforms have been shown to be up-regulated in inflammatory and neuropathic pain states [28, 154–156]. Lidocaine blocks all sodium channel isoforms but differences in isoform sensitivity to lidocaine could be an explanation for efficacy in various different pain models.

Animal studies demonstrate that systemic lidocaine changes conduction in neurons of the dorsal horn, dorsal root ganglion and hyper-excitable neuromas without affecting normal nerve conduction [23, 135, 157]. Cell membranes of injured peripheral nerves express sodium channels with unusual density and produce persistent spontaneous discharges that maintain a central hyper-excitable state [20]. Ectopic discharges can be initiated along the injured nerve, in the dorsal root ganglion, and in peripheral neuromata [157–161]. Lidocaine inhibits these aberrant electrical discharges at concentrations well below those necessary to produce conduction blockade in nerves. Dorsal-horn neurons are more sensitive to lidocaine compared with peripheral neurons [135]. The high susceptibility of hyper-excitable neurons to lidocaine may be attributed to the changed expression of sodium channels during nerve injury [28].

Analgesic effects are thought to be mediated by the inhibition of Na channels, NMDA, and G-protein-coupled receptors that lead to the suppression of spontaneous impulses generated from injured nerve fibres and the proximal dorsal root ganglion [23, 117, 159, 162].

While the main mechanism of the therapeutic action of lidocaine is considered to be blockade of voltage-gated channels, lidocaine may also have a desensitizing effect on TRP channels. This may reflect the prolonged analgesic effects sometimes seen that outlast the expected presence of lidocaine in the tissue [163].

Anti-inflammatory effects are attributable to attenuation of neurogenic inflammation and subsequent blockade of neural transmission at the site of tissue injury. Lidocaine inhibits the migration of granulocytes and release of lysosomal enzymes which leads to decreased release of pro- and anti-inflammatory cytokines [146, 162, 164–167]. Animal studies demonstrate that these anti-inflammatory effects of lidocaine are mediated by inhibition of VGSC, G-protein-coupled receptors and ATP-sensitive potassium channels.

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The anti-hyperalgesic effect of lidocaine is presumed to result from the suppression of peripheral and central sensitization through a combination of nocioceptor blockade, dampening of the neuro-inflammatory response to pain, NMDA receptor inhibition and modulation of the glycinergic system [25, 168–173]. Low dose lidocaine (10 μM) enhances and high dose (1 mM) inhibits glycinergic signalling [174]. The lidocaine metabolite, N-ethylglycine (NEG) is a substrate of the glycine reuptake transporter so it competes with endogenous and synaptically released glycine for reuptake leading to increased extracellular and synaptic glycine levels [172]. This would explain why NEG has been shown to induce analgesia in rodent models of neuropathic and inflammatory pain but has minor effects on Na^+ channels [172]. The lidocaine metabolite MEGX has been shown to inhibit the glycine transporter which will also increase glycine levels [172].

2.4. A central effect of systemic lidocaine

On-going input from peripheral nociceptors which is blocked by local anaesthetics is used to explain dependence of pain syndromes on peripheral inputs [175]. However, IVLT also has a central effect reducing components of pain caused by central nervous system injuries [176]. Systemically administered lidocaine has been shown to suppress capsaicin-induced hyperalgesia by a central mode of action, whilst concurrently reducing acute chemically induced pain by a peripheral mode of action [114]. Descending facilitatory pain transmission from the rostroventromedial medulla may also be suppressed by lidocaine [177, 178].

2.5. Role of IVLT in acute perioperative pain

Lidocaine infusions were described to be effective in the relief of acute post-surgical pain as early as 1961 [179]. Since then many other studies have confirmed the analgesic effects of lidocaine in patients with acute pain, such as Stayer's report on the safe and successful use of continuous pleural lidocaine after thoracotomy in children [180]. In 2012, Sun et al. published a meta-analysis of randomized controlled trials examining systemic lidocaine for post-operative analgesia and recovery after abdominal surgery [181]. It showed a decrease in post-operative pain intensity, opioid consumption, time to first bowel movement, and hospital length of stay. The most widely used lidocaine infusion regimen was a bolus of 1.5 mg/kg lidocaine followed by an infusion of 1.5–2 mg/kg/h.

The current evidence for using IV lidocaine for perioperative pain is based on four systematic reviews and one Cochrane review [128, 182–185]. In the most recent Cochrane review Kranke et al., reviewed only perioperative studies where the IVLT had been started intra-operatively prior to incision and continued at least until the end of surgery. Forty studies met the inclusion criteria. Primary outcomes measures required were pain score (0–10 cm, 0–100 mm visual analogue scale, (VAS), numeric rating scale (NRS), post-operative ileus, and functional gastrointestinal recovery (either time to defaecation, time to first flatus, or time to first bowel movement/sounds). Secondary outcomes sought included length of hospital stay, functional post-operative neuropsychological status scales, surgical complications (such as post-operative infections, thromboembolism, wound breakdown), patient satisfaction (satisfaction survey), cessation of the intervention, intra-operative opioid requirements, opioid

requirements during the postoperative period and any adverse events (e.g. post-operative nausea and vomiting (PONV), death, dysrhythmias or signs of lidocaine toxicity).

Intravenous lidocaine administration was initiated with a bolus dose in 64% of the included trials. The subsequent infusion ranged from 1 to 3 mg/kg/h but most commonly was 1.5 mg/kg/h. In five studies, no bolus dose was given prior to the start on the intravenous infusion of lidocaine [186–190].

The lidocaine infusion was terminated either at skin closure or the end of the surgical procedure [45, 186, 188, 190–206]; 1 h after surgery/skin closure [207–212]; 1 h after arrival in the post anaesthesia care unit (PACU) [213]; 4 h post-operatively [214]; up to 8 h post-operatively (or at PACU discharge whichever occurred earlier) [187]; after a total of 12 h [215]; 24 h post-operatively [216–223]; 48 h post-operatively [215, 224–226]; or on the day of return of bowel function or, at the latest, on the fifth post-operative day [189]. One study did not report the cessation time for the lidocaine infusion [227].

In this review, intravenous lidocaine was used in a variety of surgical procedures such as abdominal surgeries, tonsillectomy, orthopaedic, cardiac, and ambulatory surgeries. It was found to be useful only in abdominal surgery, where anaesthetic and opioid requirements were significantly reduced in the perioperative period. Several studies reported a decrease in pain intensity (pain at rest, cough, and movement), opioid requirements, and opioid-related side-effects, such as PONV. A decrease in the duration of post-operative ileus was also seen and is attributed to a combination of opioid-sparing effect, anti-inflammatory actions, decreased sympathetic tone and the direct effect of lidocaine on intestinal smooth muscle. These benefits did not translate to expedited discharge from PACU nor have a positive effect on ambulatory surgeries.

2.6. Role of lidocaine in paediatric acute perioperative pain

None of the studies included in the most recent Cochrane review for IVLT in acute pain management were paediatric. There is currently only one randomized controlled trial of IVLT in a paediatric acute pain population [228]. This study demonstrated decreased hospital stay, decreased rescue analgesia requirements, decreased cortisol levels and earlier return of bowel function with IVLT (1.5mg/kg bolus followed by 1.5mg/kg/h infusion) compared to placebo followed abdominal surgery. Until further evidence of paediatric analgesic efficacy and safety are available doses have to be translated from adult practice. It is not clear what dose regime and plasma concentration provide the best analgesic efficacy for particular surgical models of pain. Pain management remains an off-label indication for the use of IVLT, and the paediatric continuous infusion dosing quoted in the drug information documentation (0.5–3 mg/kg/h) refers to its use as an anti-arrhythmic agent.

The author uses IVLT as an adjunct in preventative multimodal analgesia for major paediatric (non-infant) surgical procedures where a regional or neuraxial analgesia technique has to be avoided or is contra-indicated. Typical procedures include scoliosis surgery, laparoscopic abdominal surgery and external frame fixator procedures. Lidocaine infusion

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regimes are typically 1 mg/kg bolus dose followed by an infusion with 2 mg/kg/h started prior to incision and continued until just after surgical closure. With extensive surgical times, the IVLT is decreased to 1.5 mg/kg/h after 8 h. It is essential to understand that there is little data to confirm the appropriate dosing and safe lidocaine levels in the paediatric population. However, clinical evaluation would suggest that the use of intravenous lidocaine therapy, in this manner, has beneficial effects on paediatric post-operative pain, opioid requirements and child/youth sense of wellbeing, especially in the first 24 h. In an attempt to determine appropriate research questions and outcome measures we have retrospectively reviewed 24 paediatric scoliosis cases. Twelve children undergoing idiopathic scoliosis correction (posterior instrumentation and fusion only) between January 2012 and March 2014, where intra-operative IV lidocaine infusion was administered were compared against twelve matched controls. The lidocaine group received a total dose of 14.17 ± 2.39 mg/kg, given over 6.45 ± 0.74 h. Both groups were comparable with respect to age, gender, body mass index (BMI), number of levels instrumented and surgical duration. Morphine consumption within the first 48 h post-operatively was significantly lower in the IVLT group [229]. Despite the small sample size and the retrospective nature of this case matched chart review the significant opioid-sparing effect in the post-operative period with the use of intra-operative IV lidocaine infusion merits further study. Prospective, randomized controlled trials are recommended.

2.7. Role of lidocaine in preventative analgesia

In many studies, the analgesic effect has persisted after the lidocaine infusion was discontinued, which suggests prevention of peripheral and/or central hypersensitivity [209, 211]. Perioperative lidocaine has been found to have a preventive effect on post-operative pain for up to 72 h after abdominal surgery [211]. A randomized, double-blind, placebo-controlled study of 36 adult patients undergoing breast cancer surgery showed that perioperative intravenous lidocaine (bolus of IV lidocaine 1.5 mg/kg followed by a continuous infusion of lidocaine 1.5 mg/kg/h) was associated with decreased incidence and severity of chronic pain after breast surgery. Two (11.8%) patients in the lidocaine group and 9 (47.4%) patients in the control group reported CPSP at 3 months follow-up ($P = 0.031$) [209]. Secondary hyperalgesia (area of hyperalgesia over length of surgical incision) was significantly less in the lidocaine group compared with control group (0.2 ± 0.8 vs. 3.2 ± 4.5 cm; $P = 0.002$). The authors concluded that IV perioperative lidocaine decreases the incidence and severity of CPSP after breast cancer surgery siting prevention of the induction of central hyperalgesia is a potential mechanism [209].

2.8. Multi-disciplinary team management of children with chronic pain

Chronic pain is pain that persists for more than 3 months and often years beyond the expected time to heal from injury, surgery or onset of a painful condition. It occurs in one in five adults and is a significant cause of suffering and disability worldwide. Although mainly a disease of adults, it does occur in children and youths with slightly more than one child/youth in every twenty reporting a chronic pain issue. A Canadian study of 495

schoolchildren aged 9–13, reported that more than half reported having experienced at least one recurrent pain (headache, stomach pain or 'growing pains'). 46% of this population reported a 'long-lasting' pain, however, the authors classified 6% as having chronic pain [230]. A Statistics Canada health report identifies chronic pain among 2.4% of males and 5.9% of females aged 12–17 years [231].

Typical types of chronic pain seen in children and youths include headaches, complex regional pain syndrome (CRPS), recurrent abdominal pain, limb and other musculoskeletal pains. Girls are three times more likely to report chronic pain than boys [232, 233]. Abdominal pain is significantly more likely to be reported by girls and limb pain (or growing pains/muscle aches) is significantly more likely to be reported by boys [230, 233, 234]. Although prevalence of chronic pain in school children varies from 9 to 32% [235, 236] and is on an increase [234], the reported prevalence exceeds the prevalence of school aged children seeking medical care for pain [237]. Cross-sectional and/or retrospective studies may not reflect the true picture and call for more longitudinal research to establish the actual prevalence and impacts of ongoing pain in children and youths has been advocated [238].

Some children with severe chronic pain embark on a downhill spiral of decreased physical, psychological and social functioning [239]. This includes loss of mobility with inability to participate in physical or sporting activities, poor sleep, difficulty concentrating on school work, school absenteeism, social isolation and family stress [240]. As chronic pain persists, the child can experience increased pain intensity, distress, sadness, anxiety, depression resulting in very poor quality of life [241]. The impact of chronic pain on the family matches the adverse impact experienced by families caring for children at home with severe cerebral palsy or birth defects [242–244]. Direct and indirect costs such as loss of earnings, adaptations to housing, over-the-counter medications and care assistance managing a child with chronic pain are considerable [245–248].

When entangled in the disordered lifestyle associated with chronic pain the child/youth and their family require coordinated integrated care to affect a recovery. The multi-disciplinary team management approach, based on pharmacology, physiotherapy and psychology (the 3P approach), is now well established to be the standard of care for children with chronic pain. This method involves looking beyond a child's pathology in isolation and engages multiple specialists to optimize the child/youth's psychological and emotional wellbeing, physical function and pharmacological therapy [247, 249–251]. This process requires adoption of a self-management approach and reduced reliance on medical investigation and intervention. Children and youth with significant pain-related disability have been shown to derive significant improvements in functional ability after participating in an intensive pain rehabilitation program employing daily physical, occupational and psychological therapies [247, 248, 252, 253].

Multi-disciplinary treatment goals are targeted to each individual child/youth after careful consideration of the medical history, pain history, examination and relevant investigations. How each therapeutic modality of care is balanced is dependent on the individual child and takes into consideration the type and duration of pain, as well as the impact of pain on particular biopsychosocial aspects of the child's life. Early recognition and appropriate '3P'

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management is the key to success. Within the context of the coordinated multi-disciplinary approach, IVLT can serve as a useful adjunct to concurrent physical, and psychological interventions to manage chronic pain in children and youths [133, 254, 255]. IVLT needs to be explained and utilized in a way that does not negate the multi-disciplinary teams attempts to promote self-management and de-medicalization.

Determining or predicting suitability for successful pharmacological treatment requires attention to a number of factors. It is essential to consider any available evidence (often lacking especially in the paediatric population), drug responsiveness (matching the predicted mechanism of action of the drug with the pathophysiology of the pain condition), side effect profile, goals of therapy and the possible impact of the pharmacological intervention to the holistic plan of self-management and return to function for the individual child/youth. One of the goals of therapy is a shift away from a change in the pain rating and pain responsiveness to restoration of physical and social functioning. For some children pharmacological therapy is not required to achieve this goal. Timing of pharmacological intervention is also important. For some children ensuring that self-management strategies and attempts at return to function are initiated prior to pharmacological intervention may decrease a reliance on medications to initiate or promote change. Not all children and youths will have a predictable or positive response to the types of medications used in chronic pain. Some will require a trial of more than one type of pharmacological agent. To minimize side-effect profiles only the lowest effective dose should be used. Different pharmacological agents may have to be used in a tiered proportional manner, balancing risk versus benefits but with the over-riding aim to improve quality of life. As the simplest most appropriate pharmacological strategy should be trialled first it is important to briefly discuss topical lidocaine.

2.9. The use of topical lidocaine therapy in paediatric chronic pain

For the purpose of this review topical lidocaine refers to q12h 5% lidocaine patch or compounded 5% lidocaine applied under an occlusive dressing (12 h on, 12 h off) administered daily. Topical lidocaine should only be applied to intact skin over a localised painful area. It is assumed that topical lidocaine works by blocking sodium channels on C, A-delta [256] and A-beta nerve fibres [257]. Allodynia is a prominent component of neuropathic pain, which is A-beta mediated and driven by central sensitization [80]. Topical lidocaine reduces nociceptor discharge at the level of the skin, to enable a light mechanical stimulus to induce a sense of touch, not pain. The analgesic effects of topical lidocaine probably do not require anaesthesia to the skin [258]. When lidocaine patches are used according to the recommended dosing instructions, only 3 ± 2% of the dose applied is expected to be absorbed. Repeated application of three lidocaine patches, used for 3 days simultaneously (12 h on, 12 h off), indicates that the lidocaine concentration does not incrementally increase with ongoing daily use. Pain relief from topical lidocaine occurs despite the extremely low systemic lidocaine plasma levels achieved. These plasma levels range from 0.13 to 0.23 μg/ml [259, 260], which is approximately one-tenth of the effective level obtained with IVLT. Despite this, neuropathic pain patients achieve pain relief from topical lidocaine [259, 261–267]. Lidocaine patches also produce analgesia in patients with painful diabetic neuropathy [268], Complex regional pain syndrome (CRPS) [269] and non-neuropathic conditions such as osteoarthritis and low-back pain [261, 270–273]. Systemic side effects are extremely rare and topical lidocaine is therefore

recommended as a first-line therapy for all children and youths with localized peripheral neuropathic pain or CRPS and definitely before consideration of IVLT.

2.10. Selection criteria for the use of IVLT in paediatric chronic pain

Lidocaine's short serum half-life of 120 min dictates that the analgesic effect disappears a few hours after treatment so this should completely preclude its use for chronic pain issues. However, prolonged relief has been reported in animal models [274] and in some non-randomized [255, 275] and randomized trials [175, 276, 277]. The Canadian Pain Society states that "intravenous lidocaine infusions are generally safe and can provide significant pain relief for 2–3 weeks at a time" [278]. The 2012 neuropathic pain interventional guidelines by Mailis and Taenzer issue a Grade B recommendation for IV lidocaine at 5–7.5 mg/kg, with relief expected to last in the range of hours to 4 weeks [279]. Clinical studies show analgesic effects of intravenously administered sodium channel blockers especially in pain conditions where hyperalgesia is prominent [114, 139, 143, 144, 276, 277, 280–282]. Chronic pain conditions, in which reports of IVLT have been beneficial include peripheral nerve injury [283], neuropathic pain [7, 16, 274, 276, 279, 284–286], CRPS [255, 287], headaches [133, 288, 289], cancer therapy, spinal cord injury [176] and fibromyalgia [290].

There is a distinct lack of evidence to support the use of IVLT for paediatric chronic pain management. Criteria and dosing guidelines are institutionally formulated based on clinical experience, but equate with dose regimes previously reported to manage chronic pain in adolescents and young adults [133], see **Table 3**.

1.	Child/youth is fully integrated into multi-disciplinary care
2.	Their pain syndrome is considered to be lidocaine-responsive
3.	The pain is not amenable to the use of topical lidocaine
4.	Patients have no contra-indication to the use of systemic lidocaine such as major cardiac dysfunction, liver dysfunction, renal impairment, seizure activity, or allergy to amide local anaesthetics
5.	Child/youth capable of verbally communicating analgesic response and symptoms of potential local anaesthetic toxicity.
6.	A high-acuity environment capable of providing continuous ECG monitoring, oxygen saturation, and frequent blood pressure measurements, plus access to healthcare personnel skilled in resuscitation and airway management.

Table 3. BCCH institutional selection criteria for initial IVLT in children/youth.

2.11. IV lidocaine infusion protocol at BC children's hospital

Initial infusion:

- Location: post-anaesthetic care unit
- Monitors: as dictated by CPSBC guideline

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- Loading dose: 1 mg/kg bolus
- Infusion: 5 mg/kg delivered over 1 h
- Total dose: 6 mg/kg (loading dose + infusion)

IVLT should only be administered within a high-acuity environment such as a paediatric intensive care unit, high-acuity unit, step-down unit, or post-anaesthetic care unit.

The College of Physicians and Surgeons of British Columbia published out of hospital Pain Infusion Clinic guidelines in 2014. The guidelines are intended only for the treatment of adults, and to the best of our knowledge, no such guidelines exist for the paediatric population. Of note, they require two appropriately trained nurses or one anaesthesiologist plus one nurse to be present in the room at all times during a lidocaine infusion, as well as one-to-one nursing for the first hour of the infusion. If the patient remains stable and not overly sedated, then the nursing ratio can be dropped to one nurse per two patients. An anaesthesiologist must be present on site until the patient is suitable for discharge. Required equipment includes an ECG monitor, suction, oxygen source and delivery systems, intravenous supplies, emergency medications, a light source, and emergency power and lighting. Lidocaine infusions are to be administered by a programmable device with a locked control panel and delivered via a dedicated intravenous line. Loading doses are to be given only by an anaesthesiologist. Patient and vital sign monitoring should be performed every 5 min for the first 15 min, every 15 min for the next 45 min, and then every hour until the infusion is complete, then 30 min after discontinuation of the infusion [291].

2.12. Selection criteria for repeat IVLT in paediatric chronic pain

There is also a distinct lack of evidence to support the use of repeated IVLT for chronic pain management. The following criteria and dosing guidelines are also institutionally formulated based on clinical experience, see **Table 4**.

1.	Child/youth is fully integrated into multi-disciplinary care
2.	The pain syndrome is lidocaine-responsive based on previous lidocaine infusion.
3.	The pain is not amenable to the use of topical lidocaine
4.	The child/youth demonstrates some improvement in functional activity following on from previous lidocaine infusion
5.	Child/youth has no contra-indication to the use of systemic lidocaine such as major cardiac dysfunction, liver dysfunction, seizure activity, or allergy to amide local anaesthetics.
6.	Child/youth capable of verbally communicating analgesic response and symptoms of potential local anaesthetic toxicity.
7.	A high-acuity environment capable of providing continuous ECG monitoring, oxygen saturation, and frequent blood pressure measurements, plus access to healthcare personnel skilled in resuscitation and airway management.

Table 4. BCCH selection criteria for repeat systemic lidocaine therapy in child/youth.

Second infusion:

- Location and monitors as for initial infusion
- Loading dose: 1 mg/kg bolus
- Infusion increased to 7 mg/kg over 90 min
- Total dose: 8 mg/kg (loading dose + infusion)
- Time between infusions: usually a month

Third infusion:

- Location and monitors as above
- Loading dose: 1 mg/kg bolus
- Infusion increased to 9 mg/kg over 90–120 min
- Total dose: 10 mg/kg (loading dose + infusion)
- Time between infusions: usually a month

2.13. Continuous subcutaneous lidocaine therapy

If IVLT is effective or partially effective, the patient can be started on a 5-day continuous subcutaneous (SC) infusion if pain is hampering for restoration of function/physical activity (**Table 5**). SC infusions use an elastomer pump which delivers a set volume of lidocaine per hour (depending on the pump used), usually 5 ml/h, which approximately equates with 2 mg/kg/h using 2% lidocaine for a patient who is 50 kg. The infusion only runs whilst the patient is awake so that they can self-report any symptoms, which may suggest lidocaine toxicity.

1.	Child/youth is fully integrated into multi-disciplinary care
2.	Their pain syndrome is lidocaine-responsive.
3.	The pain is not amenable to the use of topical lidocaine
4.	Child/youth has no contra-indication to the use of systemic lidocaine.
5.	Child/youth capable of verbally communicating analgesic response and symptoms of early local anaesthetic toxicity.
6.	The child has previously experienced a lidocaine infusion in a high acuity environment without complication.
7.	The child/youth demonstrates some improvement in functional activity following on from previous lidocaine infusion/s.
8.	The child/youth and their principal carer demonstrate the ability to follow safety instructions.
9.	Appropriate homecare support, immediate telephone contact with healthcare team and follow-up are in place.

Table 5. BCCH selection criteria for subcutaneous lidocaine therapy in child/youth.

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2.14. BCCH experience of lidocaine infusions for chronic pain

Of 336 new children/youth seen as out-patients by one pain physician in our institution over a 6.5 year time frame, only 45 (13%) were considered appropriate for trial of IVLT; 36/45 (80%) of these patients were females. The diagnoses, IVLT treatments and outcomes for these 45 children/youth are shown in **Tables 6** and **7**.

	n (%), N = 45
Diagnosis	
Complex regional pain syndrome (CRPS)	24 (53%)
Neuropathic pain	7 (16%)
Headaches	4 (9%)
Diffuse muscular/whole body pain	4 (9%)
Other	6 (13%)
IVLT sessions	
1 IVLT session only	19 (42%)
2 IVLT sessions	19 (42%)
3 IVLT sessions	6 (13%)
4 IVLT sessions	1 (2%)

Table 6. Diagnoses and number of IVLT treatments received as part of 3P treatment package.

Improved outcome reported	**Success ratio***
Physical functioning	32/43 (74%)
Pain	32/45 (71%)
Mood related to pain	22/31 (71%)
School	16/26 (62%)
Sleep	17/29 (59%)
Social functioning	8/21 (38%)

*Number of patients reporting improvement / number reporting issue prior to treatment.

Table 7. Improved outcomes reported by patients following 3P treatment including intravenous lidocaine therapy (IVLT).

It is clear that not all children and youth with chronic pain are candidates for IVLT. Focus should be on pain conditions with a neuropathic or central element. However, when appropriately selected, and integrated in multi-disciplinary care, IVLT can be part of the reason that children and youth experience less pain facilitating healthier sleep, improved physical activities, and return to school. It is also clear that not all children/youth considered appropriate for IVLT respond positively. This needs to be clearly outlined with a plan of management prior to embarking on an IVLT therapy.

2.15. The mechanism and effects of IVLT in chronic pain

The specific effects of IVLT rely on the pharmacological action of lidocaine. However, other elements of care are also critically important especially the psychosocial dynamics of the diagnosis and treatment process. Three mechanisms contribute to improvement in a patient's pain or functioning; the specific or intended effects of treatment, natural history of the disease and non-specific effects of treatment [292].

One non-specific treatment effect likely to improve treatment outcomes is high pre-treatment expectations of recovery [293–299]. Factors shown to modulate pre-treatment expectations include dispositional optimism [300–302], sex [297, 303], age [303], education level [297, 303], clinician-patient interactions [304] and degree of psychological distress [297]. Expectations can be enhanced by verbal suggestions, conditioning and imagery [299]. Influences likely to improve treatment outcomes include high expectations, no pre-existing mood disorder, low levels of anxiety, acceptance of the chronic pain diagnosis, a desire to get better, a need to return to a previous level of functioning, motivation and good clinician-to-child relationship and trust in the healthcare team.

Children and youth with chronic pain will require a lot of effort on the part of the clinicians to establish trust as they have met with many previous different healthcare workers; they may have been given mixed messages regarding the aetiology of pain, and potentially exposed to a negative encounter (not feeling believed that they have pain, lack of empathy, poor communication, lack of appropriate help).

To gain a child or youth's trust and that of their parents requires good communication [304–306]. This demands devotion of enough time to listen and extract a precise pain history, use of appropriate language and terminology, developmentally appropriate explanation of concepts [307] as well as understanding family culture, beliefs, hopes and fears. Trust necessitates that; potentially embarrassing questions are asked separately and in confidence and that the healthcare team convey empathy and expertise/credibility in chronic pain management. Introducing appropriate humour into the dialogue also helps to establish good rapport. It is also important to explain to a child/youth with ongoing pain that the healthcare team will attempt to minimise any pain on examination. During the initial assessment good education, establishing an agreed workable goal-directed and achievable management plan positively alters patient outlook as well as responses to treatment [298, 308]. Communicating positive expectations of treatment also contributes to decreased pain and improved functioning [309–311].

Psycho-social effects such as sadness, frustration, anxiety, anger, catastrophization or depression are the detrimental factors that are associated with continuation or worsening of pain. If these psychological factors remain unrecognized and untreated, they become barriers to the onward progress of any chronic pain management plan.

Without the evidence of a randomised double-blind placebo controlled trial, it is not easy to discern the over-riding beneficial therapeutic modality in the chronic pain case series presented. It could be argued that IVLT responsiveness, in tandem with good rapport and trust in the healthcare team, represents a placebo response. Such a response is defined as 'the psychobiological response seen after administration of a non-therapeutic modality'. Placebo

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treatments have known effects on endogenous pharmacology, as well as the cognitive and conditioning systems in humans [312–319]. The placebo response rate is higher in children compared with adults [320, 321]. Patient expectations and the doctor-patient relationship contribute to placebo analgesia responses and are unique to the individual [322]. The respiratory centres, serotonin secretion, hormone secretion, immune responses and heart function are also involved in the biological response to placebo analgesic treatments [319]. There is evidence that endogenous endorphins play a role as some placebo analgesic responses are reversed with naloxone [318, 323]. When considering non-analgesia placebo responses, dopamine also plays a major role [324]. Placebo response, or not, IVLT is a short intervention with minimal side effect profile, it is a worthwhile component of therapy that helps effect a turnaround to recovery in a child or youth who may have had pain and disability for many months prior to the intervention.

In an effort to increase the effectiveness of multi-disciplinary pain programs, more research is needed to further investigate pharmacological advances, psychological therapies and physiotherapy techniques that work for different ages, different types of pain and at different times in the chronic pain journey. It is clear that we also need to research and adopt clinical strategies aimed at optimising placebo and non-specific treatment effects in the paediatric population.

3. Conclusion

Intravenous lidocaine has peripherally and centrally mediated analgesic, anti-inflammatory and anti-hyperalgesic properties [176] with minimal side-effect profile if used at appropriate dosing in properly selected children/youths. It is ideally placed to be a useful adjunct in perioperative pain management to improve comfort, reduce opioid requirements and reduce the attendant opioid side effect profile.

The analgesic properties reflect the variable dose, time dependant, multimodal aspect of its action on voltage-gated Na channels and other receptors that affect nociceptive transmission pathways [23, 24, 45, 117, 146–148, 159, 162]. The anti-inflammatory effects of lidocaine are attributable to attenuation of neurogenic inflammation and subsequent blockade of neural transmission at the site of tissue injury [146, 162, 164, 165, 167].

The anti-hyperalgesic effect of lidocaine, through suppression of peripheral and central sensitization also diminishes the neuro-inflammatory response to pain [25, 168–171, 173, 325]. A basic understanding of pain physiology and pathophysiology is essential to understand how these three beneficial components of IVLT are effecting this response.

Evidence from adult work and clinical experience with paediatric patients indicates that IVLT is a modality, which needs to be considered for major surgical procedures where a regional technique is not indicated. This has promise to improve post-operative pain, reduce opioid requirements and prevent central sensitisation. More work needs to be done to demonstrate effective dose response and plasma levels of lidocaine that are associated with analgesic efficacy for different surgical pain models and whether continuation of the infusion into the post-operative phase will further reduce acute or chronic postsurgical pain.

Chronic pain of childhood is an extremely complex condition that can have devastating effects on physical, psychological and social functioning. The inter-disciplinary team management approach, based on pharmacology, physiotherapy and psychology, is the standard of care for children with severe or ongoing chronic pain. IVLT is a modality that may be considered when the history and examination findings confirm a central, neuropathic or CRPS aspect of the presenting pain. The current lack of evidence-base to support this recommendation does necessitate full disclosure of risks and benefits for informed consent and shared decision making to occur. IVLT must be explained in the right context as a small part of the multi-disciplinary care package, which focuses on de-medicalization and self-management. A singular focus on reducing pain intensity without considering improvement in physical activity, social functioning and overall quality of life is distinctly misguided. Treatment expectations need to be clear that IVLT is used to improve comfort to enable physiotherapy/physical functioning to go ahead and needs to be performed in tandem with all the other multi-disciplinary aspects of care.

Pain clinicians need to engage in large multi-site randomised controlled trials to provide the evidence-base to determine that IVLT is indeed an effective and safe treatment option in acute preventative multimodal analgesia and as an adjunct in the multi-disciplinary care of chronic pain in the paediatric population.

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