The efficacy and safety of intravenous lidocaine for analgesia in the older adult: a literature review

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Abstract

Opioids remain the mainstay of analgesia for the treatment of moderate to severe acute pain. Even in the young, the use of opioids can be associated with an increased incidence of post-operative complications such as respiratory depression, vomiting, pruritus, excessive sedation, slowing of gastrointestinal function, and urinary retention. The need to manage acute pain in the older patient is becoming more common as the population ages, and increasingly older patients are undergoing more major surgery. Medical conditions are more common in older people and can result in the requirement of systemic analgesia for fractures, malignancy, nociceptive or neuropathic pain and peripheral vascular disease. Effective pain control can be difficult in older patients as there is a higher incidence of coexistent diseases, polypharmacy and age-related changes in physiology, pharmacodynamics and pharmacokinetics. Consequently, due to the fear of respiratory depression in older people, this leads to inadequate doses of opioid being given for the treatment of their pain. Lidocaine has analgesic, anti-hyperalgesic and anti-inflammatory properties and is metabolized by the liver which is limited by perfusion, and heart failure or drugs can alter this, affecting its clearance. Therefore, there are concerns regarding safety in older patients as plasma concentrations have both intersubject and intrasubject variability. The aim of this literature review is to assess the efficacy and safety of intravenous lidocaine as an adjuvant in pain management for the older patient. In total, 12 studies fulfilled the criteria. Lidocaine infusions were found to reduce pain scores and be opioid sparing in abdominal and urological surgery, in patients with opioid-refractory malignancy pain, neuropathic pain and critical limb ischaemia. Patients with malignancy were more likely to develop adverse effects, but no patients required treatment for lidocaine toxicity.

Keywords

Efficacy, pain, intravenous, lidocaine, older patient

Introduction

Opioids remain the mainstay of systemic analgesia for the treatment of moderate to severe acute pain.¹ Due to the increased risk of cardiovascular, gastrointestinal and renal adverse effects from non-steroidal anti-inflammatories, they can also be preferentially used in the management of mild pain for the older patient.¹ The need to manage acute pain in the older patient is becoming more common as the population ages, and increasingly older patients are undergoing more major surgery. Medical conditions are more common in older people and can result in the requirement of systemic

analgesia for fractures, cancer, nociceptive or neuropathic pain and peripheral vascular disease.¹ Effective pain control can be more difficult compared to younger patients as there is a higher incidence of coexistent

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diseases and polypharmacy. There are also age-related changes in physiology, pharmacodynamics, pharmacokinetics and altered responses to pain.¹ Even in the young, the use of opioids can be associated with an increased incidence of post-operative complications, such as respiratory depression, nausea and vomiting, excessive sedation and slowing of gastrointestinal function.² Studies looking at age-related changes in pain tolerance indicate that there is a reduced ability to tolerate intense pain, as well as having a prolonged recovery from hyperalgesia.¹ However, for the older patient, the changes in the number or function of opioid receptors means that sensitivity can be increased by 50%.¹ As a result of this significant interpatient variability and the fear of respiratory depression, this can lead to inadequate doses of opioid being given for the treatment of their pain.¹

Lidocaine is an amide local anaesthetic that has analgesic, anti-hyperalgesic and anti-inflammatory properties. Analgesic effects are thought to be mediated by the suppression of spontaneous impulses generated from injured nerve fibres and the proximal dorsal root ganglion. This occurs by the inhibition of sodium channels, *N*-methyl-D-aspartate receptors and G-protein-coupled receptors. The anti-inflammatory effects are attributable to the blockade of neural transmission at the site of tissue injury, resulting in the attenuation of neurogenic inflammation and to the intrinsic anti-inflammatory pathway. It inhibits the migration and release of granulocytes and lysosomal enzymes leading to decreased release of pro- and anti-inflammatory cytokines. This results in the suppression of peripheral and central sensitization, resulting in its proposed anti-hyperalgesic effect.³ There may, however, be concerns regarding safety in the older patient as altered physiology and polypharmacy can reduce metabolism or alter clearance thereby increasing the plasma concentration of free lidocaine.³ While age-related decreases in clearance of bupivacaine and ropivacaine have been shown, this has not yet been demonstrated for lidocaine.¹ The aim of this study was to conduct a narrative literature review to assess the efficacy and safety of intravenous lidocaine as an adjuvant in the management of pain in the older patient.

Method

Identification of studies

A search was performed to identify studies published between January 1956 and May 2016. Databases of peer-reviewed literature, including NCBI, Ovid, ScienceDirect and MYED University of Edinburgh Library were searched. Reference lists of retrieved articles, including case reports, previous literature or systemic reviews were also screened for additional studies.

Search strategy

Search terms 'elderly' and 'older' were originally used; however, no studies were found specifically assessing pain in the older patient. This was expanded by only including terms 'lidocaine', 'pain' and 'intravenous'. Studies were excluded if the mean age was under 60 (Figure 1).

Data extraction

Data were extracted from the articles according to the headings in Table 1, and identified trials were examined for internal validity using the Oxford Quality Score criteria.¹⁶

Results

Search results

Abdominal surgery (*n*=4)

1. Infusion of 1 mg/minute commenced in the post-anaesthesia care unit and continued for 24 hours.⁴
2. Lidocaine bolus of 2 mg/kg 30 minutes before surgery followed by an infusion of 3 mg/kg/hour peri-operatively.⁵
3. Lidocaine bolus of 1.5 mg/kg before induction of anaesthesia and an infusion of 2 mg/kg/hour until abdominal wall closure.⁶
4. Lidocaine bolus of 1.5 mg/kg immediately after induction of anaesthesia followed by an infusion of 1.5 mg/kg/hour terminating 60 minutes after skin closure.⁷

Studies 2⁵ and 3⁶ also compared epidural lidocaine. All three interventions (placebo, intravenous and epidural) were separate, and therefore no patient received both intravenous and epidural lidocaine concurrently.

Pain scores in three studies showed statistically significant reductions in the visual analogue scale (VAS) scores when comparing intravenous lidocaine to saline placebo.⁵⁻⁷ One showed a non-significant difference in the VAS score of 45.4 in the placebo group versus 26.1 in the lidocaine group.⁴

Two of the studies^{5,7} calculated statistically significant reductions in morphine requirements with one revealing a non-statistically significant reduction of 23.8%.⁷ No reduction in morphine requirements were found in one study.⁴

Total hip replacement (*n*=1)

1. Lidocaine bolus of 1.5 mg/kg 30 minutes before surgical incision followed by an infusion of 1.5 mg/kg/hour stopped 1 hour after skin closure.⁸

Table 1. Included studies with quality score, patient groups, L regimens, pain scores and opioid consumption.

Study	Jadad score	No. of patients	Dose and duration of lidocaine infusion	Pain scores	Post-operative opioid Consumption
Harvey et al. ⁴ Colorectal surgery	5	22 Lidocaine (11) Control (11)	1 mg/minute post-op for 24 hours	No difference at 6 hours ($p=0.24$), 18 hours ($p=0.26$) with trend towards significance in L group at 24 hours ($p=0.08$)	Increased total morphine consumption in lidocaine group, not statistically significant ($p=0.4525$)
Kuo et al. ⁵ Colorectal surgery	4	60 Epidural (20) Intravenous lidocaine (20) Control (20)	Epidural L: 2 mg/kg + 3 mg/kg/hour IV Lidocaine: 2 mg/kg + 3 mg/kg/hour 30 minutes before surgery until end of surgery	VAS scores at rest, 2 hours and 4 hours, and during coughing at 12 hours were significantly lower in IV L compared with the C group $p<0.001$	33% reduction in total PCEA morphine consumption 0–72 hours in the IV L group in comparison with the control group ($p<0.01$)
Staikou et al. ⁶ Colorectal surgery	4	60 Epidural (20) Intravenous lidocaine (20) Control (20)	Epidural lidocaine: 1.5 mg/kg + 2 mg/kg/hour IV Lidocaine: 1.5 mg/kg + 2 mg/kg/hour before induction of anaesthesia until end of surgery	VAS scores at rest at 1 hour, 2 hours and 4 hours, and coughing at 1 hour, 2 hours and 4 hours ($p=0.004$) and 48 hours ($p=0.023$) significantly lower in the IV L compared with the C group	Reduction in PCEA morphine consumption when comparing IV lidocaine versus control but not statistically significant ($p=0.054$)
Koppert et al. ⁷ Colorectal surgery	4	40 Lidocaine (20) Control (20)	1.5 mg/kg + 1 mg/kg/hour 30 minutes pre-skin incision until 1 hour post-op	No difference in VAS scores at rest, but VAS scores significantly lower on movement at 48 hours and 72 hours post-op ($p<0.01$)	35% reduction in overall morphine consumption at 0–72 hours ($p<0.05$)
Martin et al. ⁸ Total hip arthroplasty	5	58 Lidocaine (28) Control (30)	1.5 mg/kg + 1.5 mg/kg/hour after induction until 1 hour post-op	No difference at rest or movement at 24 hours, 48 hours or 3 months	Total morphine consumption less in lidocaine compared to control (43 mg vs 46 mg, respectively), although not significant $p=0.97$
Groudine et al. ⁹ Retropubic prostatectomy	5	40 Lidocaine (20) Control (20)	1.5 mg/kg + 3 mg/minute if >70 kg or 2 mg/minute if <70 kg after intubation until 1 hour post-op	66% reduction in total pain score in the L group ($p<0.0001$)	50% reduction in morphine requirements in PACU in the L group ($p<0.05$). No difference in opioid consumption after PACU.
Insler et al. ¹⁰ Coronary artery bypass graft	5	89 Lidocaine (44) Control (45)	1.5 mg/kg + 30 µg/kg/minute after induction until 48 hours post-op	No difference in VAS scores between groups at 4–96 hours	Reduced fentanyl consumption in lidocaine group compared to control from 0 to 96 hours (620 µg vs 689 µg, respectively), although not statistically significant ($p=0.244$)

(Continued)

Table 1. (Continued)

Study	Jadad score	No. of patients	Dose and duration of lidocaine infusion	Pain scores	Post-operative opioid Consumption
Thomas et al. ¹¹ Opioid-refractory pain in malignancy	0	61 Lidocaine (61)	1–2 mg/kg + 1 mg/kg/hour	44% reported a complete cessation of pain, 82% reported a major reduction in pain, 8% had partial response and 10% gained no benefit. No statistical test calculated	Not applicable as opioid-refractory patients
Sharma et al. ¹² Opioid-refractory pain in malignancy	4	50 Lidocaine (25) Control (25)	2 mg/kg + 2 mg/kg over 1 hour	Significant decrease in mean severity of pain over 14 days ($p < 0.001$), and increased duration of pain relief ($p < 0.001$)	Significant decrease in frequency of rescue medication in lidocaine group compared to control ($p = 0.01$)
Baranowski et al. ¹³ Post-herpetic neuralgia	4	24 Lidocaine 1 mg/kg (24) Lidocaine 5 mg/kg (24) Control (24)	All patients received saline placebo, 1 mg/kg lidocaine and 5 mg/kg lidocaine for 2 hours, 1 week apart	No change in VAS scores. Significant reductions in area of allodynia for 1 mg/kg ($p < 0.05$) + 5 mg/kg ($p < 0.001$). Significant reduction in brush stroke pain for both doses of lidocaine ($p < 0.05$)	Not assessed
Viola et al. ¹⁴ Diabetic neuropathy	5	15 Lidocaine 5 mg/kg (15) Lidocaine 7.5 mg/kg (15) Control (15)	All patients received saline placebo, 5 mg/kg lidocaine and 7.5 mg/kg lidocaine for 4 hours, 4 weeks apart	Significant reduction in pain scores up to 28 days ($p < 0.05$ for 5 mg/kg + $p < 0.001$ for 7.5 mg/kg)	Nil difference found (no p-value calculated)
Vahidi et al. ¹⁵ Critical limb ischaemia	4	40 Lidocaine (20) Control (20)	Lidocaine 2 mg/kg for 30 minutes versus morphine 0.1 mg/kg, over 30 minutes	No p-values calculated. 22.5% reduction in VAS scores at 30 minute for lidocaine group	Not assessed

IV: intravenous; L: Lidocaine; VAS: visual analogue scale; C: control; PCEA: patient-controlled epidural analgesia; PACU: post-anaesthesia care unit.

Figure 1. Flow diagram of identification of individual studies for inclusion.

There was neither a significant reduction in 48-hour morphine consumption nor a reduction in pain scores at rest or movement compared to placebo.

Radical prostatectomy surgery (n = 1)

1. Lidocaine bolus of 1.5 mg/kg immediately before induction of anaesthesia, followed by an infusion of 3 mg/minute or 2 mg/minute (for over and under 70 kg in weight, respectively) terminating 60-minutes after skin closure.⁹

There was a significant reduction in 24-hour pain scores ($p=0.001$) compared to saline placebo, and a clinically significant reduction in post-anaesthesia care unit morphine requirement with overall morphine consumption being 50% less.

Coronary artery bypass graft (n = 1)

1. Lidocaine bolus of 1.5 mg/kg immediately after induction of anaesthesia followed by an infusion of 30 µg/kg/minute up to 48 hours post-operatively compared to an unknown placebo.¹⁰

There was neither a significant reduction in VAS pain scores nor fentanyl requirements post-operatively.

Palliative care (n = 2)

1. Lidocaine bolus of 1–2 mg/kg over 20 minutes, followed by an infusion of 1 mg/kg of unknown duration.¹¹

In total, 82% of patients reported a major reduction in pain (decrease in three or more points on a scale of 0–10), with 44% of all patients reporting their pain as 0/10. No statistical tests were done on these data.

2. Lidocaine bolus of 2 mg/kg over 20 minutes, followed by an infusion of 2 mg/kg over 1 hour.¹²

Statistically significant ($p<0.0001$) reduction in pain scores, increase in duration of pain relief ($p<0.0001$) and requirement of rescue medication was lower ($p=0.01$) after lidocaine.

Neuropathic pain (n = 2)

1. Placebo versus 1 mg/kg and 5 mg/kg of lidocaine over 120 minutes, 1 week apart for post-herpetic neuralgia.¹³

Significant reductions in brush stroke pain and in the size of area of allodynia ($p<0.05$ for 1 mg/kg and

$p < 0.001$ for 5 mg/kg), but little differences in VAS scores between the three groups.

2. Placebo versus 5 mg/kg and 7.5 mg/kg of lidocaine over 4 hours every 4 weeks for diabetic neuropathy.¹⁴

At days 14 and 28, there were significant reductions in severity of pain between the placebo and lidocaine infusions ($p < 0.05$ for 5 mg/kg and $p < 0.001$ for 7.5 mg/kg), but no significant differences between the two doses of lidocaine infusions.

Critical limb ischaemia (n = 1)

1. Bolus of 2 mg/kg lidocaine over 5 minutes versus standard 0.1 mg/kg intravenous morphine.¹⁵

A one-degree difference in the mean VAS score was considered to be clinically significant, and there was a mean difference of 2.25 at 15–30 minutes. No statistical tests were done to calculate whether this was statistically significant.

Post-operative nausea and vomiting (n = 2)

1. Statistically significant ($p < 0.01$) reduction in morphine-related post-operative nausea and vomiting (PONV) for the group receiving intravenous lidocaine.⁵
2. No association between improvement in PONV between the lidocaine and placebo groups.⁷

Neurological side effects (n = 3)

1. Transient confusion
2. Light-headedness
3. For patients with opioid-refractory cancer pain, 52% developed neurological side effects.¹² However, 36% of patients in the placebo group also experienced neurological side effects and was therefore calculated as not statistically significant. None required treatment.^{6,14}

Plasma lidocaine concentrations (n = 3). Lidocaine toxicity is considered to be $>5 \mu\text{g/mL}$, and three of the studies measured plasma levels.

1. Bolus of 1.5 mg/kg and an infusion of 1.5 mg/kg/hour: plasma levels varied, predominantly being $<3.8 \mu\text{g/mL}$, although one patient had levels of $4.5 \mu\text{g/mL}$ after the bolus.⁷
2. Bolus of 1.5 mg/kg and an infusion of 2 mg/minute, if $<70 \text{ kg}$ or 3 mg/minute if 70 kg or above: plasma levels within a non-toxic range of 1.3– $3.7 \mu\text{g/mL}$.⁹

3. Infusion of 1 mg/kg or 5 mg/kg over 2 hours: first dose had mean levels below $2.5 \mu\text{g/mL}$ and the latter had mean levels of up to $11 \mu\text{g/mL}$.

No adverse effects were commented on in any of the studies.¹³

Discussion

Lidocaine is an amide local anaesthetic that has many pharmacological properties. It has various mechanisms of action as an analgesic resulting from the interaction with sodium channels and direct or indirect interaction with different receptor and nociceptive transmission pathways. There is also a peripheral anti-hyperalgesic effect on somatic pain and central effect on neuropathic pain with the consequent block of central hyperexcitability.¹⁷

This review shows that an infusion of lidocaine may have a useful effect in older patients undergoing abdominal surgery. This is consistent with the ability of lidocaine to ease visceral pain in animal models via inhibitory effects on visceromotor reflexes evoked by colorectal distension.¹⁸ The regimen of 1 mg/minute over 24 hours showed no benefit, which is consistent with the known tachyphylaxis that is associated with lidocaine.¹ A meta-analysis reviewing the appropriate end time for peri-operative intravenous lidocaine in the general population also concluded that continuing beyond 60 minutes after surgery has no additional benefit.¹⁹ The lowest lidocaine concentration at 1 mg/kg/hour used by Koppert et al.⁷ produced significant reductions in pain on movement but not at rest, and a 35% reduction in opioid requirements. Kuo et al.,⁵ and Staikou et al.⁶ used a similar duration as Koppert but higher lidocaine doses, resulting in improved clinical effects of reducing VAS scores at rest. Out of the four studies, it appears that an infusion of the shortest duration but a higher dose (2 mg/kg bolus + 3 mg/kg/hour infusion) provides both significantly reduced pain at rest and movement post-operatively, but also significantly reduced opioid requirements. This is important in older patients because their physiology alters the pharmacodynamics and pharmacokinetics of the drug interactions which can result in increased peak concentrations of opioids as high as a 50% increase.¹ These results were also associated with reductions in opioid requirements and pain levels in urological surgery. However, their regimen of 2 mg/minute for patients under 70 kg, and 3 mg/minute for those $>70 \text{ kg}$ would not be advisable in older patients as it can produce widely varying doses per kg body weight and therefore plasma levels. This could result in inadequate pain control or inadvertent toxicity. While there have been no meta-analyses on the effects of intravenous lidocaine

after abdominal surgery for the older patient, there have been four since 2008 studying the general population. They also concluded that intravenous lidocaine peri-operatively reduces post-operative pain and opioid requirements, although further research is required for optimal dosage.^{20–23}

Older patients are more likely to undergo orthopaedic procedures than younger patients; however, this study⁸ does not appear to indicate that peri-operative lidocaine infusions are of any benefit. The investigators surmised that the lack of effect was due to the low dose of lidocaine infused, and, consequently, the lower mean plasma concentration of 2.1 µg/mL. Contradicting this is the study by Tanelian and Maciver²⁴ which established that the clinically effective pain-relieving serum lidocaine concentrations are 2–10 µg/mL. However, it may depend on the dose infused as animal studies have shown a difference in response to small, moderate, and large doses.²⁵ Therefore, further studies need to be done and analyzed before stating that a lidocaine infusion is of no benefit for older patients undergoing orthopaedic procedures.

Neither could it be demonstrated that lidocaine infusions are beneficial in older patients undergoing a coronary artery bypass graft (CABG) procedure as there were no statistically significant results. The authors determined that in order for the reduction in VAS scores to yield a $p < 0.05$, 2190 patients would have been required to be in the study. They concluded that larger doses may be necessary.

Post-operative chronic pain is a well-documented surgical complication, and while there may be no evidence for its efficacy in reducing acute post-operative pain in surgery other than colorectal or urological, it could be useful in reducing the risk of chronic post-operative pain. A small meta-analysis reviewing intravenous lidocaine in patients undergoing breast surgery found that while there was no significant benefit acutely, it appeared to attenuate the risk of chronic pain.²⁶

Both studies looking at the effect of intravenous lidocaine on cancer pain in opioid-refractory patients appear to show that it could be a useful adjuvant in achieving pain relief. The incidence of adverse features was markedly higher in the cancer patients compared to all the other studies, and 52% of patients had one side effect, with a significantly higher chance of having two or more side effects when compared to placebo. In contrast, only two other patients in all the studies developed adverse features of lidocaine toxicity. Serum levels were not taken in these studies, so it is impossible to comment on whether the increase in adverse side effects is because cancer patients are more likely to have higher levels due to physiological, pharmacodynamics or pharmacokinetic changes. Lidocaine is 90% metabolized by the cytochrome p450 enzyme in the

liver, and, if this is inhibited, it could result in an increase in the plasma concentration which is particularly relevant due to its narrow therapeutic index.²⁷ Malignancy or cancer therapy may affect these variables, thereby altering plasma levels. There is currently no data or studies on local anaesthetic levels in cancer patients.

Studies reviewing lidocaine infusions for the treatment of neuropathic pain showed variable improvements.^{13,14} The first study¹³ acknowledged older patients are more likely to have significant cardiovascular pathology and so lower dose infusions were administered, which would be the equivalent of 0.5 mg/kg/hour and 2.5 mg/kg/hour when compared to the surgical studies. The second study¹⁴ used the equivalent of 1.25 mg/kg/hour and 1.875 mg/kg/hour but the total dose administered was higher due to there being a longer infusion time. The latter study showed significant reductions in pain scores of up to 28 days, with the former showing reductions in the area of allodynia and brush stroke pain but not actual VAS scores. These results indicate that a lidocaine infusion may be beneficial in treating neuropathic pain in older patients but over a longer infusion time so a higher dose can be utilized without causing toxic plasma levels.

The study assessing lidocaine in the treatment of critical limb ischaemia did not do any calculations to determine whether their results were statistically significant. However, their results do indicate that a lidocaine infusion is superior with a 22.5% reduction in mean VAS scores 30 minutes after presentation. This would be consistent with its mechanism of action of blocking high-voltage sodium channels of stimulated nerves, with ischaemic pain being thought to be due to stimulation of nociceptors within ischaemic muscle.¹⁵

It is not possible to compare my findings with results from other meta-analyses among the general population on the use of intravenous lidocaine in the management of non-surgical pain as there are currently none.

Plasma lidocaine concentrations and adverse effects

The goal of an infusion is to achieve a steady state concentration within the therapeutic and non-toxic range. Weight-based lidocaine regimens in studies have shown that 1.33–3 mg/kg/hour achieved adequate plasma concentrations of 2–5 µg/mL.²⁸

Following prolonged intravenous infusions, lidocaine exhibits time-dependent, or nonlinear, pharmacokinetics. In patients receiving prolonged lidocaine infusions after myocardial infarction, lidocaine concentrations continued to rise for about 48 hours, and the half-life was prolonged.²⁸ This supports the literature

that older patients should have a shorter infusion duration but with a higher dose with concurrent cardiac monitoring. To prevent adverse effects, it would therefore be advisable to have a weight-based dose calculation and adjustments made according to a patient's past medical history. While the lidocaine infusion was of significant benefit in cancer patients, the increased prevalence of neurological adverse effects means further studies should be done on optimal dosing and plasma levels. Only one meta-analysis among the general population could be found reviewing the safety of intravenous lidocaine peri-operatively. Despite there being no major adverse events, due to the scarcity of studies that systemically assessed the incidence of adverse effects among surgical patients, definitive conclusions could not be made.²⁰

Limitations

The main limitations were the lack of studies specifically looking at efficacy of intravenous lidocaine in the older patient and also the small sample size. The revised literature searches meant that while on average patients were over 60, younger patients would still be included.

Conclusion

Lidocaine infusions of short duration have a clear advantage in older patients undergoing abdominal and urological surgery or being treated for opioid-refractory pain in malignancy, neuropathic pain or critical limb ischaemia. It provides significant pain relief, reduces concurrent opioid consumption and can decrease opioid-induced nausea and vomiting. It is also well-tolerated, inexpensive, easy to apply and has a similar efficacy to epidural local anaesthesia in colorectal surgery. Further studies reviewing its efficacy in the management of non-surgical pain would be beneficial as there has been little research so far. This could be particularly pertinent in the management of complex neuropathic and opioid-refractory pain in malignancy. In addition, further studies are needed to accurately determine the optimum dose and duration of infusion required in colorectal and urological surgery, as well as providing definitive evidence of its lack of efficacy in cardiac and orthopaedic surgery.

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