Clinical Trial/Experimental Study

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Effect of intravenous lidocaine infusion on long-term postoperative pain after spinal fusion surgery

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Abstract

Background: Intravenous lidocaine infusion is known to reduce postoperative pain for days or weeks beyond the infusion time, and plasma half-life in several types of surgical procedures.

Objectives: To evaluate the effect of intravenous (IV) lidocaine infusion on long term postoperative pain intensity for 3 months in patients undergoing spinal fusion surgery.

Study Design: Prospective randomized, double-blinded study.

Setting: Assiut University Hospital, Assiut, Egypt.

Methods: Forty patients undergoing spinal fusion surgery were randomized into 2 equal groups (n = 20 in each). Patients in the lidocaine group received IV lidocaine at a dosage of 2.0 mg/kg slowly before induction of anesthesia, followed by lidocaine IV infusion at a rate of 3.0 mg/kg/h until the end of surgery. Patients in the control group received an equal volume of normal saline. The following data were assessed: pain by Visual Analog Score (VAS) at 1 hour, 6 hours, 12 hours, 24 hours, 48 hours, at discharge time, and at 1 month, 2 months, and 3 months post-operation, time to first request for additional analgesia, and total morphine consumption in 24 hours.

Results: Lidocaine significantly reduced the postoperative pain score (VAS) for up to 3 months ($P < .05$), and significantly reduced morphine consumption (4.5 mg vs. 19.85 mg) in the 1st 24 hours postoperative. Lidocaine also significantly, prolonged ($P < .05$) the time to first request for additional analgesia (9.56 ± 2.06 hours vs 1.82 ± 0.91 hours).

Conclusion: Intra-operative lidocaine, when given intravenously as a bolus followed by an infusion, significantly decreased long term postoperative back pain intensity in patients undergoing spinal fusion surgery.

Abbreviations: μm/L = micromoles/L, ASA = American Society of Anesthesiologist, FBSS = failed back surgery syndrome, IV = intravenous, LA = local anesthetic, MEGX = mono-ethyl-glycine-xylidide, SD = Standard deviation, VAS = Visual Analog Score.

Keywords: lidocaine intravenous, long term back pain, spinal fusion

1. Introduction

Spinal fusion is a painful surgery, and control of postoperative pain is difficult. Several studies have indicated that appropriate pain treatment protocols reduce postoperative morbidity, improve the results of the surgery, and decrease hospital costs.[1]

A likely, common mechanism for many adverse outcomes in patients with spinal fusion surgery is the systemic inflammatory response to surgical tissue injury.[2] In addition, the activation of glial cells in the surgical wound stimulates the production of cytokines in the central nervous system, which can induce peripheral, and central sensitization through generation of nitric oxide, free radicals, and excitatory amino acids, possibly also causing chronic, and neuropathic pain.[3] The role of inflammatory cytokines is also well recognized in the process of secondary hyperalgesia, and central sensitization.[4]

Obtaining adequate analgesia after major surgery is a problematic issue, and postoperative pain still imposes a major burden of suffering on surgical patients. Intravenous (IV) patient-controlled opioids the mainstay modality in acute surgical pain treatment, expose the patients to potentially serious side effects.[5]

Lidocaine which developed in the year 1948 is the first amino amide-type short-acting local anesthetic (LA). Originally, it was used mainly via the IV route as an antiarrhythmic drug. Lidocaine has a very short half-life, and a favorable safety profile, and is therefore the LA of choice for continuous IV administration.[6]

The perioperative administration of systemic IV lidocaine has been shown to be an effective method in postoperative pain management with a favorable effect on pain scores, opioid consumption (opioid-sparing effects), and recovery after surgery without any clear evidence of harm.[5]

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Lidocaine has analgesic, and anti-inflammatory effects that are induced by reduction of cytokines production through inhibition of neutrophil activation, and the analgesia may persist even after plasma concentration reduction.[7] Lidocaine IV administration produces an analgesic effect in various pain states, such acute postoperative pain, and neuropathic pain.[8]

Lidocaine infusion has been shown to be successful in controlling pain, whereas other agents have failed. The opioid sparing properties of IV lidocaine infusion added to its analgesic, and anti-hyperalgesic properties make lidocaine infusion a viable option for pain control in chronic opioid users.[9]

1.1. Aim of the work

The primary objective of this study was to evaluate the postoperative Visual Analog Score (VAS) for 3 months, following intraoperative use of lidocaine IV infusion, during adult spinal fusion surgery. The secondary objective was to calculate postoperative (24 hours) morphine consumption.

2. Methods

2.1. Study design and patients

This was a prospective, double-blinded, and randomized clinical study. The study was approved by our local hospital Institutional Review Board (Faculty of medicine ethical committee Assiut University). The study protocol was registered with the Clinical trials.gov (ID: NCT03030560).

Ethical considerations: written, and informed consent was obtained from all patients after thorough explanations about study purpose, design, and procedures to each patient. All collected data was confidential, and was used for the purpose of scientific research only. Every research participant had the complete right, and freedom to withdraw at any time from the study with no negative consequences on the medical service provided to him or her.

2.2. Inclusion criteria

Subjects were patients over 18 years old, both male, and female, American Society of Anesthesiologist (ASA) I, II, and III undergoing spinal fusion surgery (single, and double level). Exclusion Criteria: subjects were excluded if they met any of the following criteria: previous spine surgery, morbid obesity (BMI > 40), spine metastatic tumor, allergy to an amide LA, or morphine sulphate, heart block, renal, or liver dysfunction, or substance abuse disorder, or chronic opioid use.

2.3. Randomization

Randomization was performed using lidocaine group, and control group registers, which were placed in sealed envelopes prior to study initiation, and opened prior to anesthesia by a physician who prepared the IV solution, and identified it with the patient number, according to the envelope drawn. The solution was handed to another physician, blind to the prepared solutions' content, who was responsible for the anesthesia. The solution volume was equal. The responsible investigator remained blind to the chosen group until the end of the study.

2.4. Study groups

Forty four patients were randomly allocated into 2 groups of equal size to receive either lidocaine infusion (Lidocaine group), or 0.9% sodium chloride infusion (Control group).

Lidocaine group (n = 22) patients received a loading dose of IV lidocaine 2 mg/kg slowly just before induction of anesthesia, then the lidocaine infusion started at a rate of 3 mg/kg/h Control group (n = 22) patients received an equal volume of 0.9% sodium chloride (both the loading, and the infusion).

The infusion in both groups was initiated at the time of anesthesia induction, and continued until the end of the operation.

2.5. Anesthesia technique

General anesthesia was induced by propofol 2.5 mg/kg, and cisatracurium 0.15 mg/kg to facilitate orotracheal intubation. Patients were then assigned to either the lidocaine, or control group by closed-envelope randomization. In both the groups, anesthesia was maintained with isoflurane in oxygen/air mixture at sufficient concentration to maintain systolic blood pressure within the limit of 20% baseline value. All patients received 60 mg ketorolac IV infusion after induction of anesthesia, and fentanyl 1.5 μg/kg IV before skin incision. Acetaminophen (paracetamol) 1gm was given by IV infusion to all patients before extubation. Reversal of residual muscle relaxant was accomplished using neostigmine, and atropine at the end of the operation. Patients were monitored with continuous electrocardiography, and pulse oximetry, and intermittent non-invasive blood pressure measurements every 5 minutes.

2.6. Postoperative pain control

In the first 24 hours postoperative; patients were given Ketorolac 30 mg slowly IV (diluted to 10 mL), and paracetamol 1 g injection for 8 hours. Morphine 0.1 mg/kg slowly IV was given as rescue analgesia when VAS was ≥4, or if the patient requested additional analgesia. A maximum of 3 doses of IV morphine were prescribed, with a minimum 8 hours interval between the 2 consecutive injections. After 24 hours post-operation; paracetamol 1 g, and ketorolac 10 mg for 8 hours were given orally for 2 weeks.

2.7. Data collection

Patient's characteristics, and surgical data including age, gender, weight, height, duration of surgery, and duration of hospital stay. Postoperative pain evaluation during rest was assessed by VAS (0 = no pain, 10 = most severe pain). The score was recorded at the following times: immediately at 1 hour; 6 hours; 12 hours; 24 hours; at discharge time; 1 month; 2 months, and 3 months post-operation. Time to the first request for analgesia, and the total dose of rescue analgesia (morphine) in the first 24 hours after surgery was recorded. The long-term follow-up of postoperative back pain for 3 months was conducted through the outpatient orthopaedic clinic, or by telephone.

2.8. Sample size calculation

A sample size calculation was performed based on a previous study.[10] To be able to detect a significant difference in pain score of 2 between the 2 groups. With an estimated standard deviation (SD) of 2.2, and an α of 0.05 in 20 patients of each group would yield 80% power. Four cases were added to the sample size to compensate for violation of the study protocol, or potential dropouts.

2.9. Statistical analysis

Collected data were analyzed using the statistical package IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. Data with continuous variables were expressed as mean ± SD, and compared using a paired t-test, if normally distributed, and by Mann–Whitney *U* test, if not normally distributed. Differences were considered statistically significant if a *P* value <.05 was obtained.

3. Results

Forty four patients were enrolled in the study, randomly allocated to 2 groups, with 22 patients in each; 4 patients were excluded from the study. One patient in the lidocaine group developed convulsions during injection of the loading dose, and 1 refused to complete the study; while in control group 2 patients refused to complete the study as shown CONSORT Statement for Reporting Trials.

3.1. Patient's characteristics and operative data

There were no significant differences observed between lidocaine group, and control group ($P > .05$) for age, sex, weight, height, ASA classification, operative time, and type of operation (number of fusion levels).

3.2. Length of hospital stay

The mean values of hospital stay was significantly lower ($P = .001$) in the lidocaine group (3.15 ± 1.08 days) when compared to that of the control group (4.55 ± 1.31 days) as shown in Table 1. The mean value of total lidocaine dose given to each patient in lidocaine group was 210.9 ± 12.16 mg/h.

3.3. Visual analogue score

The mean values of postoperative VAS pain score were significantly lower in the lidocaine group in the first 48 hours post operation, and during the study period up to 3 months after the operation ($P < .05$). At the time of discharge from the hospital, mean VAS values were 1.05 ± 0.88 in the lidocaine group, and 1.00 ± 1.33 in the control group. Long term postoperative follow up of the patients for 3 months revealed that VAS remained significantly lower in lidocaine group ($P < .05$) as shown in Figure 1, and Table 2.

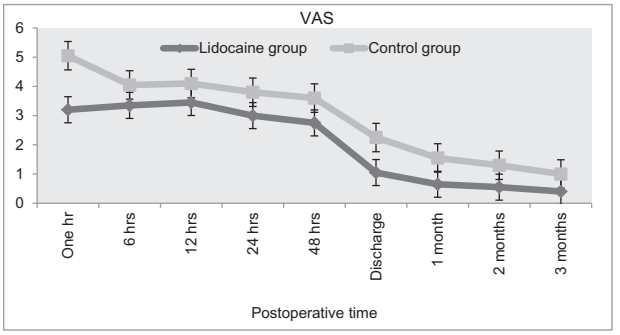

Figure 1. Visual analog pain score for postoperative 3 months in the studied groups.

3.4. The time to first analgesic request

The mean time to first analgesic request was significantly longer in lidocaine group (9.56 ± 2.60 hours) while it was 1.82 ± 0.91 hours in the control group ($P < .001$). Rescue analgesia: the mean total dose of morphine consumed by the patients during the first 24 hours post operation in the lidocaine group (4.5 ± 5.37 mg) was significantly lower than that consumed in the control group (19.85 ± 8.96 mg) with $P < .001$.

4. Discussion

This study evaluated the effect of intra-operative IV infusion of lidocaine on long term postoperative pain by assessment of VAS pain score for 3 months after spinal fusion surgery compared to control group. The data revealed that VAS pain score were significantly, lower in the lidocaine group in the first 48 hours post operation, at time of discharge from the hospital, and after 3 months from the operation. The VAS for postoperative 48 hours, and 3 months after discharge in both groups were statistically but not clinically significant; it was mild, or moderate pain. The mean values of time to first request of additional analgesia (morphine) were significantly longer in the lidocaine group than in control group, and consequently the mean total dose of IV morphine consumed by the patients in the first 24 hours post-operation were significantly lower in the lidocaine group.

Our data are consistent with other studies in which IV lidocaine was found to improve the early postoperative analgesia in different types of surgery, including complex spine surgery,[2]

Table 1

Patient's characteristics, operative time, and duration of hospital stay.

	Lidocaine group (n = 20)	Control group (n = 20)
Age, y	41.20 ± 7.60	42.50 ± 5.20
Sex (male:female)	11:9	13:7
Weight, kg	76.50 ± 8.80	82.00 ± 7.00
Height, cm	164.82 ± 8.13	168.52 ± 9.61
ASA (I:II:III)	2:17:1	1:18:1
Operative time, min	108.00 ± 25.75	110.50 23.72
Type of surgery		
One level	8	7
Two levels	12	13
Length of hospital stay, d	3.15 ± 1.08	4.55 ± 1.31

ASA = American Society of Anesthesiologist
Values were expressed as mean ± SD, ratio and number.

Table 2

Visual analogue pain score for postoperative 3 months in the studied groups.

Postoperative time	Lidocaine group (n = 20)	Control group (n = 20)	*P*
1 hour	3.2 ± 1.1	5.05 ± 1.27	<.001*
6 hours	3.35 ± 0.81	4.05 ± 0.82	.01*
12 hours	3.45 ± 0.60	4.10 ± .85	.01*
24 hours	3.00 ± 0.64	3.80 ± 0.83	.001*
48 hours	2.75 ± 0.85	3.60 ± 0.50	.003*
Discharge	1.05 ± 0.88	2.25 ± 1.8	.014*
1 month	0.65 ± 0.81	1.55 ± 1.43	.016*
2 month	0.55 ± 0.75	1.30 ± 1.41	.02*
3 months	0.40 ± 0.75	1.00 ± 1.33	.03*

Values were expressed as mean ± SD.
* Significant *P* value .05.

pediatric fusion surgery, subtotal gastrectomy,[11] laparoscopic abdominal gynecologic surgery,[12] outpatient laparoscopy,[13] inguinal herniorrhaphy,[14] and upper abdominal surgery.[15]

On the other hand, some studies have failed to demonstrate a significant analgesic effect of IV lidocaine during the postoperative period after laparoscopic renal surgery,[16] abdominal hysterectomy,[17] and total hip arthroplasty.[18]

A likely, common mechanism for many adverse outcomes in patients with spinal fusion surgery is the systemic inflammatory response to surgical tissue injury.[2] In addition, the activation of glial cells in the surgical wound stimulates the production of cytokines in the central nervous system, which can induce peripheral, and central sensitization through generation of nitric oxide, free radicals, and excitatory amino acids, possibly also causing chronic, and neuropathic pain,[3] The role of inflammatory cytokines is also well recognized in the process of secondary hyperalgesia, and central sensitization.[4]

The potent anti-inflammatory effects of IV lidocaine are mediated by inhibition of *N*-methyl-d-aspartate receptors, and by reduction of cytokine production through inhibition of neutrophil activation.[2] The analgesia produced by lidocaine may persist after reduction in its plasma levels, favoring the theory of blockade in neuronal conduction.[19] Lidocaine's metabolite, mono-ethyl-glycine-xylidide (MEGX), may also exert an analgesic effect.[20] Systemic lidocaine has been reported to reduce the MAC of inhalational anesthetics, postoperative pain, analgesic consumption, postoperative nausea, and vomiting, and the length of stay in hospital.[10]

The perioperative administration of systemic IV lidocaine has been shown to be an effective method in postoperative pain management with a favorable effect on pain scores, and both intra- and postoperative opioid consumption, and recovery after surgery without any clear evidence of harm.[5] Its effect may continue for days, or weeks, that is, beyond the infusion time, and plasma half-life, indicating that it may affect other targets in addition to voltage-gated sodium channels. This suggests lidocaine may act via a prevention of the hypersensitivity of the central, or peripheral nervous system, or both.[1]

In neuropathic, or inflammatory pain animal models, IV lidocaine is thought to exert analgesic effects by blocking specific Na^+ channels in injured nerves, or dorsal root ganglia (DRG);[21] because these channels are more sensitive to lidocaine.[22] An interesting work was conducted by Viola et al which studied the long-term effect of IV lidocaine infusion in patients with diabetic neuropathy, and they found that lidocaine infusion markedly reduced both pain severity, and quality at 14 to 28 days post infusion.[23] Similarly, Aslam et al concluded that lidocaine infusion in a dose of 5 mg/kg/h for 2 hours is both effective, and safe in reducing the chronic intractable pain in both painful diabetic neuropathy, and non-painful diabetic neuropathy patients.[24]

In this study patients in lidocaine group received a loading dose of IV lidocaine 2 mg/kg slowly, just before induction of anesthesia, and then the lidocaine infusion started at a rate of 3 mg/kg/h till the end of operation. All patients in the lidocaine group were assessed for signs of lidocaine toxicity in the postoperative period, and no patient had sign of toxicity with the exception of one patient developed convulsion during injection of the loading dose.

Investigations of the optimum concentration of lidocaine for spinal, and peripheral regional anaesthesia suggest that a high concentration >200 mm/L (μm/L) is required to block peripheral nerve fibre impulses.[25] The half maximal effective concentration of lidocaine for myelinated, and unmyelinated dorsal root axons were 232 to 228 μm/L, respectively.[26] When lidocaine is intravenously, administered in doses from 1 to 5 mg/kg, its plasma concentration ranges from 4 to 20 μm/L; therefore, the clinically effective plasma concentration of lidocaine to produce analgesia is far below that needed to block nerve impulses.[27]

In their systematic review Kranke et al (2015); found that, perioperative lidocaine infusion at rates greater than, or equal to 2 mg/kg/h was associated with decreased VAS pain scores, and opioid consumption in the first 24 hours[28] Park et al investigated the effects of IV lidocaine on neuropathic pain of failed back surgery syndrome (FBSS) which the results from abnormal impulse originated from the dorsal root ganglion, and spinal cord. The authors found that 1 mg/kg, or 5 mg/kg of IV lidocaine, and placebo improved pain in patients with neuropathic pain attributable to FBSS, but the 5 mg/kg dose was significantly, more effective in some pain items (sharp, dull, and deep pain).[29] Administration of IV bolus injection of 1.0 mg/kg lidocaine immediately, before induction of anesthesia, then a continuous infusion at a rate of 2 mg/kg/h had a significant postoperative analgesic effect in patients undergoing thyroid surgery.[30]

5. Conclusion

Our results suggest the role of lidocaine infusion as adjuncts to general anesthesia, it significantly, decreased long term postoperative back pain intensity, and delayed, and reduced the need for rescue analgesics, in patients that undergoing spinal fusion surgery.

6. Limitations

Small sample size is a limitation of this study which may affect our results however this sample size was similar to other study (10), another limitation is serum level of lidocaine which was not measured in this study however the loading, and maintenance dose in the present study was similar to those in previous studies (28–31) with no detectable side effects.

7. Recommendations

The authors recommend further studies to be performed on a larger sample size, and different doses may be used to detect an optimal lidocaine dose. The study recommends the intraoperative use of lidocaine IV infusion as an alternative mode of analgesia following spine surgery due to its long-term analgesic effect.

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