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Efficacy of Lidocaine Infusion for Treatment of Chronic Neuropathic Pain: A Case Control Study

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ABSTRACT

Background: Neuropathic pain is a type of chronic pain that is related to nerve damage and is defined by the International Association of Study of Pain (IASP) as "*pain caused by a disease or lesion of the somatosensory nervous system*". It remains a challenging clinical problem as pain often can be quite severe and debilitating. The rationale of this study is to find out the efficacy of intravenous lidocaine infusion for neuropathic pain management in our population as there has been no study conducted in Pakistan for this purpose. As our country has a rather low-income population and cheaper options for treatment need to be explored. **Objective:** To determine the efficacy of lidocaine infusions of 3 mg/kg in managing the chronic neuropathic pain given at 0,1, 2 and 3 weeks in comparison to the placebo infusion. **Study Design:** Case control study. **Settings:** The study was conducted in the Sheikh Zayad Hospital Lahore Pakistan. **Duration:** July 2022 to December 2022. **Methods:** 100 outdoor patients fulfilling the inclusion and exclusion criteria were enrolled after taking informed written consent and were randomly allocated to Lidocaine group (A) 3 mg/kg, diluted in 50 ml normal saline and placebo group (B) 50 ml intravenously over 30 minutes. The Lidocaine group was injected with lidocaine, intravenously over 30 minutes once a week for 4 weeks. Patients with established diagnosis of neuropathic pain, adults of both genders, age above 18 years were enrolled in this study. Their pain severity was recorded using Numerical rating scale (NRS). The data of both groups was recorded in predesigned proforma and efficacy was also noted as labelled as Yes/No for two points; 1: Decrease in pain score by at least 2 out of 10 and 2: Decrease in oral analgesics intake. **Results:** There were 50 patients in group A and B with the mean age of 53.82 years and 54.4 years respectively. Patients in group A who received an intravenous infusion of lidocaine reported less severe pain and fewer instances of breakthrough pain. No statistically significant difference (P>0.05) was discovered between NRS ratings before and after infusions in the control group despite the fact that several patients reported lower pain intensity after the infusion. The quantity of opioid used was determined for the Lidocaine and Placebo groups. Opioid in the placebo group was 0.472–0.572 g per patient, but in the Lido group it was only 0.1–0.2 g per patient which is significantly different from placebo group (p=0.0021). **Conclusion:** Lidocaine intravenous infusion (3 mg/kg daily for 4 weeks) improved short-term results of therapy, decreased the need for analgesic medication, and shortened pain score without causing major adverse effects.

Keywords: *Lidocaine, Placebo, NRS, Opioid.*

INTRODUCTION

Neuropathic pain is a type of chronic pain that is related to the nerve damage and is defined by International Association of Study of Pain (IASP) as "*pain caused by a disease or lesion of the somatosensory nervous system*".[1]

It remains a challenging clinical problem as pain often can be quite severe and debilitating. Also in most cases, neuropathic pain is associated with psychological disturbances that make management more difficult and time consuming. It has been postulated that neuropathy can occur in any form in most living beings. Population based studies have shown that prevalence of neuropathic pain is in the range of 7 to 10% based on validated screening tools for neuropathic pain.[2]

Regarding the management of neuropathic pain, efficacy of certain antidepressants, anticonvulsants, opioid analgesics and miscellaneous agents have been established in systemic reviews[3] and several evidence based guidelines have been developed.[4] Nevertheless, these studies consistently show that less than 50% of patients achieve adequate pain control in the short term and only a quarter achieve significant pain relief in the long term at 12 months.[5] This advocates further research and exploration of new treatment options.

Intravenous local anesthetic infusion has been in practice by many pain physicians for quite some time, lidocaine being most commonly used as it has a short plasma life and easily manageable side effect profile. This modality of treatment is being used in outdoor settings at many pain management centers, as studies have shown the absence of any serious side effects and established its safety.[6,7,8] Many regimens are being used at various centers all over the world depending on their departmental protocol. One of the most popular and widely used is lidocaine 3 mg/kg intravenous infusion given over 30 minutes once a week for four weeks.[6] This dose is considered to be safe for lidocaine as serious side effects have not been seen even by using the recommended maximum safe dose of lidocaine i.e. 5mg/kg.[9] It has shown promising results in many studies in overall pain control and reducing the requirement of analgesics.[2,10] However there are some studies which show quite the opposite as having no significant decrease in pain relieving medication when compared to placebo.[11]

The rationale of this study is to find out the efficacy of intravenous lidocaine infusion for neuropathic pain management in our population as there has been no study conducted in Pakistan for this purpose. As our country has a rather low-income population and cheaper options for treatment need to be explored.

METHODS

This case control study was conducted in the Sheikh Zayad Hospital Lahore from July 2022 to December 2022. Outdoor patients fulfilling the inclusion and exclusion criteria were enrolled after taking informed written consent and were randomly allocated to Lidocaine group (A) and placebo group (B). By using WHO calculator sample size is 100 (50 in each group) for study with level of significance 5%, with confidence of interval 95% and power of test was 80%. Anticipated population proportion for placebo group = 28.6%. Anticipated population proportion for lidocaine group = 50%.[12]

Patients with established diagnosis of neuropathic pain, adults of both genders, age above 18 years were enrolled in this study. However, patients with altered sensorium, history of ischemic heart disease, history of cardiac arrhythmias, history of epilepsy, patients who lost follow up before completion of the study, patients who could not take complete dose of lidocaine due to side effects, pregnant females, patients who are allergic to local anesthetic were excluded.

After the approval of the ethical committee, written informed consent was taken from the patients fulfilling the inclusion and exclusion criteria. Patients were randomly allocated to the lidocaine group and placebo group by double blind technique by using online random number generator software and allocating odd numbers to Lidocaine group (group A) and even to placebo group (group B). Their pain severity was recorded using Numerical rating scale (NRS). Their analgesics requirements were also noted. Placebo group was infused with Normal saline 50 ml intravenously over 30 minutes. The Lidocaine group was injected with lidocaine 3 mg/kg, diluted in 50 ml normal saline, intravenously over 30 minutes once a week for 4 weeks. Patients were monitored keenly for side effects. After the completion of the infusion, patients were assessed for decrease in pain score immediately after infusion and after 1 week, before the administration of the next infusion. After the completion of 4 doses, patients were assessed for reduction in pain score immediately after the last infusion and at 1 week follow up. Decrease in analgesics consumption was also documented. The data of both groups was recorded in predesigned proforma and efficacy was also noted as labelled as Yes/No for two points; 1: Decrease in pain score by at least 2 out of 10 and 2: Decrease in oral analgesics intake.

After achieving the desired number of patients, data were analyzed using SPSS version 21. Data was presented as the average decrease in NRS in both groups. Data was segregated as frequency and percentages for the categorical variables i.e., genders and efficacy. Standard deviation (SD) and mean was calculated. The Chi square test was used to calculate the efficacy in both groups. P value ≤0.05 was considered as significant.

RESULTS

There were 50 patients in group A and B with the mean age of 53.82 years and 54.4 years respectively. In group A 16 female and 34 males, however, in group B there were

7 female, and 43 males were enrolled. Patients in the Lido group had 3 mg/kg lidocaine pumped into their veins at the same time every morning, whereas those in the Control group received 50 mL of saline. The discomfort associated with was shown to be greatly alleviated by an intravenous infusion of lidocaine. Pain levels were measured to see how well lidocaine worked as an analgesic. Breakthrough pain and NRS ratings both reduced during the course of 4 weeks. Furthermore, NRS pain ratings shown in table 1 and the frequency of breakthrough pain episodes within the week were both lower in the lidocaine group from the first day of treatment onwards. Patients in group A who received an intravenous infusion of lidocaine reported less severe pain and fewer instances of breakthrough pain. No statistically significant difference (P>0.05) was discovered between NRS ratings before and after infusions in the Control group despite the fact that several patients reported lower pain intensity after the infusion shown in Table 2.

Table 1: Pain score in terms of NRS of lidocaine group before and after drug administration

Pain Score		Mean	Std. Deviation	P-value
0 Week	Lidocaine Before	7.38	1.18	.001
	Lidocaine After	7.13	0.22	
1 Week	Lidocaine Before	5.84	0.77	<0.001
	Lidocaine After	4.50	0.76	
2 Week	Lidocaine Before	4.52	0.56	<0.001
	Lidocaine After	3.90	0.72	
3 Week	Lidocaine Before	4.38	0.49	<0.001
	Lidocaine After	3.44	0.50	
4 Week	Lidocaine Before	3.25	0.39	<0.001
	Lidocaine After	1.22	0.42	

Table 2: Pain score in terms of NRS of placebo group before and after normal saline

Pain Score		Mean	Std. Deviation	P-value
0 Week	Normal Saline Before	6.66	0.24	.245
	Normal Saline After	6.14	0.23	
1 Week	Normal Saline Before	6.38	0.49	.103
	Normal Saline After	6.26	0.25	
2 Week	Normal Saline Before	6.33	0.24	.345
	Normal Saline After	5.73	0.25	
3 Week	Normal Saline Before	0.51	0.06	.456
	Normal Saline After	5.78	0.25	
4 Week	Normal Saline Before	6.09	0.19	.564
	Normal Saline After	5.58	0.19	

The quantity of opioid used was determined for the Lidocaine and Placebo groups. Opioid in the placebo group was 0.472–0.572 g per patient, but in the Lido group it was only 0.1–0.2 g per patient which is significantly different from placebo group (p=0.0021). Efficacy in terms of 1: Decrease in pain score by at least 2 out of 10 is yes and 2: Decrease in oral analgesics intake were no in the patient of group lidocaine and vice versa in group placebo which is considerable significant (p=0.001).

Table 3: Adverse outcomes recorded in lidocaine group

Adverse Outcome	Frequency	Percent %
Somnolence	17	34.0%
Dry mouth	15	30.0%
Peripheral numbness	6	12.0%
Diziness	8	16.0%
Tinnituss	3	6.0%
Chest tightness	1	2.0%

DISCUSSION

In this trial, we carefully tracked the brief pain-relieving effects of IV lidocaine in people with moderate-to-severe neuropathic pain discomfort. The therapeutic efficacy throughout pain period and the acute analgesic effect at the end of infusion were both assessed. Patients with neuropathic pain who received an intravenous infusion of lidocaine reported improved effectiveness, decreased analgesic intake, and a shorter length of feeling pain. Lidocaine infusions were given more often in this trial than previously described in individuals with persistent pain (once weekly or once every 2 days).[12] Patients who did not meet our stringent exclusion criteria were given 4 mg/kg of lidocaine intravenously once daily while their vital signs were constantly monitored. That no major adverse effects were discovered is encouraging. To determine the optimal tolerance and quantity of intravenous lidocaine infusion for a given patient with chronic pain (mostly neuropathic pain), Tan Xinran et al. infused lidocaine rapidly and heavily (1 g/hr in 30 minutes, infusion rate of 16.67 mg/mins) in 233 individuals. This experiment to determine the challenge dosage was carried out until the pain was completely relieved, adverse effects were reported, or the infusion was finished. For the first-time lidocaine infusion group of 233 patients, 53 percent had no adverse effects at all, and 46 percent experienced just minor discomfort.20 In another study, 20 patients with trigeminal neuralgia were given 5 mg/kg lidocaine (infused for 60 minutes). Lidocaine had no impact on systolic BP, diastolic BP, HR, or oxygen saturation; nevertheless, somnolence and dry mouth were noted by 32.5% of patients.[13,14] We hypothesize that variations in patients' physical condition or ethnicity account for the observed heterogeneity in the incidence of side effects among trials. Lidocaine intravenous infusion was well tolerated by neuropathic pain patients overall.

Infusions of lidocaine at a dose of 3 to 5 milligrams per kilogram have been utilized to treat chronic pain in previous research.17,20 Based on these trials, we administered a daily infusion of 4 mg/kg.[15] In the 60 individuals with neuropathic pain, there were no significant adverse events. While we support the use of intravenous lidocaine infusion treatment, we caution pain specialists and those who conduct clinical trials to do so with caution. To begin, lidocaine is known to produce arrhythmia; thus, it is important to determine whether individuals already have this condition.[16] Because the toxicity of lidocaine depends on both its dose and plasma levels, a modest infusion rate is recommended.[17] Third, the effects of drug buildup and simultaneous usage of medications on liver and kidney function should be considered. Lidocaine might be used in combination with other therapies, but the overall dosage would have to be refigured. Patients' liver and renal functions should also be assessed as required.[18,19]

Alpha-2 delta ligands, tricyclic antidepressants, tramadol, or opioids are the first line of therapy for neuropathic pain according to current standards. In addition to these drugs, neuropathic pain is often treated with nerve blocks, pulse radiofrequency, physical therapy, etc.[20] When these methods are used together, however, the therapeutic results are often disappointing. Based on our findings, intravenous infusion of lidocaine greatly improves the analgesic effectiveness of standard therapy, is quick, cheap, and safe.[13] This means that it has the potential to be used in hospitals. Lidocaine intravenous infusion has been shown to be beneficial in-patient cohorts suffering from neuropathic pain, including neuropathic pain, according to recent studies. It has also been observed that the usage of opioids and its negative side effects may be decreased by using lidocaine.[21-23]

In this work, we considered the potential mechanism by which lidocaine infusion reduces neuropathic pain discomfort. Lidocaine's short-term impact, sodium channel blockade, which closes the sodium channel of the afferent fibers at the pain site and hinders the transmission of pain signals, may account for the pain reduction seen upon completion of the infusion.[24] It was previously believed that the production of inflammatory cytokines was one of the reasons of neuropathic pain, but recent research suggests that the long-term impact of lidocaine infusion may be connected to its anti-inflammatory effects.[25] Daykin hypothesized that the anti-inflammatory effect of intravenous lidocaine was due to the blockade of nerve conduction at the tissue level with neuropathic pain, which in turn reduced neurogenic inflammation and set in motion an intrinsic anti-inflammatory pathway also suppressed peripheral and central sensitization, which led to analgesic effects, and also influenced the release of pro-inflammatory and anti-inflammatory cytokines.[26] There was evidence that N-ethylglycine, a metabolite of lidocaine, was responsible for the drug's analgesic effects. Lidocaine's therapeutic mechanism for chronic pain requires further investigation using molecular biology, cell biology, and animal tests on blood and tissue samples.[27]

We have previously used functional magnetic resonance imaging to show that people with neuropathic pain have aberrant activity in the parts of the brain that are responsible for processing emotions, anxiety, and sadness. No significant difference was discovered between Lido and Control patients on the day of discharge, suggesting that lidocaine infusion did not improve pain in lidocaine group patients.

CONCLUSION

Lidocaine intravenous infusion (3 mg/kg daily for 4 weeks) improved short-term results of therapy, decreased the need for analgesic medication, and shortened pain score without causing major adverse effects.

LIMITATIONS

Long-term data on lidocaine infusion were not included in this research, just its short-term effects. However, further study is needed to determine whether daily intravenous infusion of lidocaine (4 mg/kg for 5 days in a row) is effective for long-term pain alleviation in neuropathic pain.

SUGGESTIONS / RECOMMENDATIONS

In order for the findings to be generalizable, it is advised that a comparison study be carried out on a broad population across various hospitals and in patients receiving a range of treatments increased population

CONFLICT OF INTEREST / DISCLOSURE

No conflict of interest.

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