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Creators	Aslam, Amir, Singh, Jaipaul and Rajbhandari, Satyan

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An Observational Study on Lignocaine Infusion for Intractable Chronic Pain

Amir Aslam^{1*}, Jaipaul Singh² and Satyan Rajbhandari^{2,3}

¹University of Calgary, Alberta, Canada

²School of Pharmacy and Biomedical Sciences, University of Central Lancashire, Preston, Lancashire, UK

³Department of Diabetology and Endocrinology, Lancashire Teaching Hospital NHS Trust, Chorley and South Ribble District General Hospital, Preston Road, Chorley, UK

Abstract

Objective: This study assessed the efficacy of lignocaine infusion as a treatment for painful diabetic neuropathy (PDN) groups compared to chronic pain (non-PDN group) in challenging cases where conventional treatment is not helpful.

Methods: A total 11 patients participated in the study with 7 patients referred from pain clinic (non-PDN group) and 4 for patients referred from diabetic foot clinic (PDN group) for lignocaine infusion as a treatment for chronic pain. Both groups of participants were on multiple combination of pain medication with minimal help. All the subjects gave consent for participation and filled out McGill short form (SF) questionnaire before and after the lignocaine infusion.

Results: The results show 33% reduction of visual analogue pain score after lignocaine infusion in PDN group compared to 11% reduction of visual analogue pain score in non-PDN group. These data were statistically significant ($p < 0.05$). Similarly, there was a significant ($p < 0.05$) reduction of affective pain score with 41% after lignocaine infusion in PDN group compared to 21% in non-PDN group. In contrast, the sensory pain score reduction after lignocaine infusion was 23% in PDN group compared to 17% in non-PDN group. These data were statistically not significant ($p > 0.05$). All 11 patients had no reported adverse effects and their observations were in normal limits throughout the lignocaine infusion.

Conclusion: Overall, the study showed that lignocaine infusion is both effective and safe in reducing chronic intractable pain when conventional treatments are intolerable or not helpful. It is more effective in painful diabetic neuropathy patients compared to other causes of chronic pain.

Keywords: Painful diabetic neuropathy; Chronic pain; Lignocaine infusion

Introduction

International association for the study of pain (IASP) defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system". Neuropathic pain is caused by direct injury or damage to, or pathological change in peripheral or central nervous system. In contrast, nociceptive pain is caused by direct injury or disease caused by tissue damage [1]. Chronic pain in general defines as pain last more than 3 to 6 months [2]. Chronic neuropathic pain is very common all over the world. It is estimated that almost 6% to 8% of the general population suffer from chronic neuropathic pain [3,4]. Painful diabetic neuropathic pain is the most common type of chronic neuropathic pain.

Currently, about 380 million people worldwide are living with diabetes mellitus (DM) and it is estimated that this figure will rise up to 592 million in the year 2035 [5]. The prevalence of DM-related complications is also rising. Painful diabetic neuropathy (PDN) is a common complication of DM, affecting about 1/3rd of all patients with DM [6]. It is characterized by bilateral symmetrical distal neuropathic pain in lower extremities with varied symptoms from mild pins and needles, tingling sensation, shooting pain similar to electric shock, constant burning sensation with nocturnal exacerbation and contact hyper-sensitivity-allodynia [7]. Relentless pain and allodynia affect patients both physically and mentally and they both cause disturbance in sleep, low mood, impotence and social withdrawal. In some extreme cases the patient is unable to walk [8-10].

There are a number of trials of treatment of PDN which show some reduction of pain following treatment with either with tricyclic-antidepressants amitriptyline [11], selective norepinephrine uptake inhibitor including duloxetine [11,12], venlafaxine [13], anticonvulsants

including pregabalin [14-17], gabapentin [18,19], carbamazepine [20], topiramate [21,22] or in severe cases opioid [23]. A met analysis on efficacy on antidepressants and anticonvulsants in combination or alone showed up to 50% reduction in pain [24]. Trial with newer medication such as tapentadol which possesses dual mode of action, opioid agonists and norepinephrine uptake inhibitor show some improvement in painful diabetic neuropathy [25]. Apart from oral treatment, there are trials with some efficacy in treating PDN with topical agents including capsaicin [26] and also isosorbide mononitrate spray [27]. Despite of treatment advancement, chronic symptoms of PDN is challenging for clinicians and distressing for patient. Boulton et al followed up 39 patients with painful diabetic neuropathy over the period of 4 years and found no significant difference in intensity of pain [28]. Another 5 year follow up study on PDN with conventional treatment reported a resolve of symptoms in only 23% patients [29].

A study on chronic neuropathic pain patients with combine conventional neuropathic treatment found up to 50% response rate only [30]. Despite of treatment advances and multiple drug regime up to 50% of chronic neuropathic pain patients are resistant to conventional treatment. And some of these treatment resistant patients are in intractable pain. These challenging patients always been a challenge

***Corresponding author:** Amir Aslam, Assistant Clinical Professor University of Calgary, Family Physician at Eaton Centre Medical Clinic, 751 3rd Street, Suite 417, Calgary, Alberta, Canada, Email: AmirAslam@hotmail.com

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for physicians. Lignocaine infusion has been reported with some satisfactory response on these challenging, conventional treatment and resistant patients [31-33].

Lignocaine is a sodium channel blocker. It was first synthesized by the Swedish chemist Nils Lofgren in 1943 [34]. Lignocaine is widely used as a local anaesthetic and for peripheral nerve blocks. It has been used intravenously for the treatment of arrhythmias and also found effective in chronic neuropathic pain [35] and chronic pain disorders [36,37] and is not associated with significant side effects [38]. Lignocaine metabolizes in the liver and its elimination half-life following an intravenous bolus injection is typically 1.5 to 2 hours. However, conditions with chronic liver disease and congestive heart failure may prolong its half-life.

The potential beneficial use of lignocaine infusion as a treatment in PDN was first evaluated by Kastrup [31]. There are several studies which reported pain relief in PDN [31-33]. Despite of rapid half-life, the duration of pain relief reported post lignocaine transfusion was up to 28 days [31,32]. This could be due to the central de-sensitization effect of lignocaine along with peripheral action. The side effects in high doses of IV lignocaine can be sedation, hypotension and arrhythmia. However, studies found IV lignocaine infusion were very well tolerated and safe [31,32,38]. Lignocaine infusion is often preserved only for patients who have persistent excruciating pain and where other medications are not beneficial.

There are several pain assessment questionnaires available to assess the pain. This study used McGill short form (SF) questionnaire, which was developed by Melzack [39]. It is an easy, quick and an excellent tool to measure the quality of pain in three different aspects including sensory, affective and visual analogue score. It has been used as a measure of pain in variety of pain condition studies including painful diabetic neuropathy [32].

The aim of this study was to assess the efficacy of lignocaine infusion in patients with painful diabetic neuropathy (PDN group) compared to chronic pain patients (Non PDN group).

Subjects and methods

PDN subjects with chronic refractory pain for ($\pm$ SD) 6.5 ± 3.42 years, not responded to standard oral and topical treatment were identified from Foot Clinic at Chorley District General Hospital (CDGH). Chronic pain subjects (non- PDN) with chronic refractory pain for ($\pm$ SD) 7.75 ± 4.77 years, not responded to standard oral and topical treatment were referred for lignocaine infusion from Pain Clinic, Lancashire Hospitals NHS Trust. Both groups of patients already tried and were on multiple combination of pain medication without relief.

Both groups of subjects attended individually and admitted to coronary care unit (CCU) as a day case for 3 hours and given lignocaine infusion 0.2% (2 mg/ml), 5 mg/kg body weight over 2 hours in coronary care unit of CDGH with throughout monitoring of electrocardiogram, blood pressure, pulse and oxygen saturations. A nurse administered McGill pain short form (SF) questionnaire before and after the infusion on each subjects. All patients recalled in "neuropathy pain clinic" in 6 weeks' time. All patients gave consent for participation.

McGill SF consisted of 15 representative words from the sensory ($n=11$), affective ($n=4$) and visual analogue score (VAS). Each word descriptor was ranked by the patient on an intensity scale of 0, none; 1, mild; 2, moderate; and 3, severe. Sensory score ranged from 0 to 33, affective score ranged from 0 to 12 and VAS range from 0 to maximum 10 [39].

Statistical analysis

Data were analysed using Graph Pad software [40]. The continuous variable were normally distributed and expressed as means, $\pm$ standard deviation (SD), median and P value. The means of McGill pain score were analysed with paired Student's t-test compared before and after lignocaine infusion. Categorical data were expressed as frequency distribution and percentage of subjects groups and p value. The categorical data of were analysed by 2×2 table using Fischer's exact test. The boxplots created with descriptive statistics using Minitab statistical software (2013). The plot showed the median (dark band) along with minimum and maximum. The box represents the lower ($Q1=25\%$) and upper ($Q3=75\%$) quartile rang.

Results

Table 1 show the demographics and baseline characteristics of patients participated in the study. A total of 11 subjects participated in the study and completed the McGill SF questionnaire before and after the lignocaine infusion. The mean age ($\pm$ SD) of subject was 52 ± 13.96 years. There were total of 4 males (36%) with mean age ($\pm$ SD) 58.7 ± 15 years and 7 females (64%) with mean age ($\pm$ SD) of 49 ± 13 years. The mean duration of chronic pain ($\pm$ SD) was 7.09 ± 4.37 years. The mean sensory score before lignocaine infusion was ($\pm$ SD) 20.14 ± 7.16 compared to mean sensory score after lignocaine infusion was ($\pm$ SD) 16.5 ± 9.52 . There was significant reduction of sensory pain score after lignocaine infusion ($p<0.05$). The mean affective score before lignocaine infusion was ($\pm$ SD) 5.5 ± 3.09 compared to mean affective score after lignocaine infusion was ($\pm$ SD) 4.0 ± 3.13 . There was a significant reduction of affective pain score after lignocaine infusion ($p<0.05$). The mean visual analogue score (VAS) before lignocaine infusion was ($\pm$ SD) 7.72 ± 1.75 compared to mean VAS score after lignocaine infusion was ($\pm$ SD) 6.13 ± 2.53 . There was a reduction of VAS pain score after lignocaine infusion, however the data were statistically not significant ($p=0.053$) (Figure 1). The box plot analysis in Figure 1 shows the McGill pain score in all 3 sub-categories including sensory score, affective score and visual analogue scores (VAS) which were part of McGill SF pain score either before (A) or after (B) the lignocaine infusion in all subjects with chronic pain. Before lignocaine infusion, the sensory score mean was 20.4 ± 7.16 SD (median 20) compared to sensory score mean after lignocaine infusion was 16.5 ± 9.52 SD (median 17.5) ($p<0.014$). Before lignocaine infusion, the affective score mean was 5.5 ± 3.09 SD (median 5) compared to affective score mean after lignocaine infusion was 4.0 ± 3.13 SD (median 3.0) ($P<0.013$). Before lignocaine infusion, the VAS score mean was 7.72 ± 1.75 SD (median 8) compared to VAS score mean after lignocaine infusion was 6.13 ± 2.53 SD (median 7) ($p=0.053$). The plot also shows the median score (dark band) along with minimum and maximum score. The box represents the lower ($Q1=25\%$) and upper ($Q3=75\%$) quartile range of score. All male participants had painful diabetic neuropathy (PDN group) as a cause of pain and all female participants had non PDN cause of chronic pain. The ages in both gender- ages and groups were similarly distributed ($p>0.05$). The mean duration of pain ($\pm$ SD) in PDN group was 6.5 ± 3.42 years compared to 7.75 ± 4.77 years in Non PDN group. The duration of pain in both groups were similarly distributed ($p>0.05$). Both groups had tried a combination of medications including antidepressants, antiepileptic medications, and opioid and moreover, they were on combination of medications with unsatisfactory response.

The results also show 33% reduction of visual analogue pain score after lignocaine infusion in PDN group compared to 11% reduction of visual analogue pain score in non-PDN group. The data were statistically significant ($p<0.05$) (Figure 2). Similarly, there was

Patient No	Age Years	Gender	PDN Yes or no	Duration of pain Years	Medication tried not helped	Current pain medications	Before Lignocaine infusion			After Lignocaine infusion		
							VAS	Sensory	Affective	VAS	Sensory	Affective
1	79	Male	Yes	11	Amitriptyline, Imipramine, Carbamazepine, Capsaicin cream, Tramadol, Pregabalin, Mexiletine, GTN patch, Duloxetine, MST, Acupuncture, Alhalipoic acid, Lignocaine patch	Gabapentin, Oxycontin	7.5	8	1	3.5	3	3.5
2	60	Male	Yes	3	Pregabalin, Amitriptyline Duloxetine, Clonazepam, Durogesic patch, Oramorph PRN.	Pregabalin, Amitriptyline Duloxetine, Clonazepam, Durogesic patch, Oramorph PRN.	9	32	7	9	29	9
3	44	Male	Yes	5	Gabapentin, Butrans patch, capsaicin cream, colnazepam	Pregabalin, Amitriptyline, Topiramate	9	12	6	3	4	3
4	52	Male	Yes	7	Pregabalin, Gabapentin, topical Capsaicin, Duloxetine, BuTrans patch, Tramadol, Oxycontin,	Morphine Sulphate, Amitriptyline, Sodium Valproate	10	22	3	8	21	8
5	41	Female	No Back Pain	5	Carbamazepine, Duloxetine, Amitriptyline, Pregabalin, Ropinerole. SI joint injections, Facet joint injections, Butrans patch, TENS machine	Carbamazepine, Duloxetine, Amitriptyline, Pregabalin, Ropinerole.	8	30	9	8	29	8
6	66	Female	No Fibromyalgia	3	TENS, acupuncture, physiotherapy, Gabapentin, amitriptyline, Naproxen, Codeine, Butrans patch	Ibuprofen 400mg prn	4	20	5	3	11	3
7	53	Female	No Back pain	9	Epidural steroid injection, Gabapentin	Oxycontin, Pregabalin, Amitriptyline	7	19	4	3	7	3
8	59	Female	No Angiolipoma	7	Gabapentin, Cocodamol 30/500, SI joint injection, Facet joint injections, TENS	Carbamazepine, Duloxetine, Amitriptyline, Pregabalin, Ropinerole	9	18	4	6	15	6
9	26	Female	No Fibromyalgia	18	Amitriptyline 50 mg, Pregabalin, Gabapentin, Tramadol, psychotherapy	OxyContin, Ibuprofen, Amitriptyline, Duloxetine.	6	16	3	8	18	8
10	45	Female	No Demyelination	6	Gabapentin, Pregabalin, Nabilone, Ketamine, Butranspatch, codeine, Capsaicin cream, Lidocaine patch, Fentanyl patch, Duloxetine, Topiramate, Carbamazepine, TENS	Amitriptyline 50 mg Codeine 60 mg at night	6.5	21.5	6.5	7	17.5	7
11	54	Female	No Stump pain	4	Paracetamol , Oramorph prn, Oxycodone MR, Pregabalin, Lidocaine patches, Acupuncture, TENS, carbamazepine	Paracetamol , Oramorph prn, Oxycodone MR, Pregabalin, Lidocaine patches	9	26	12	9	27	9

Table 1: Demographics and baseline characteristics of patients participated in the study.

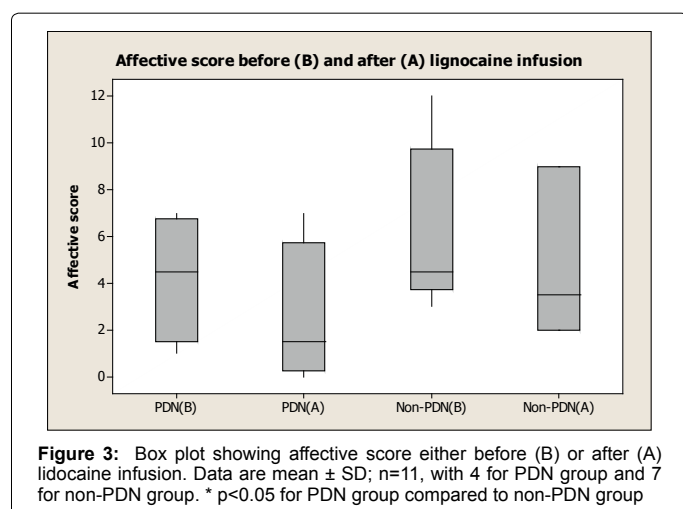
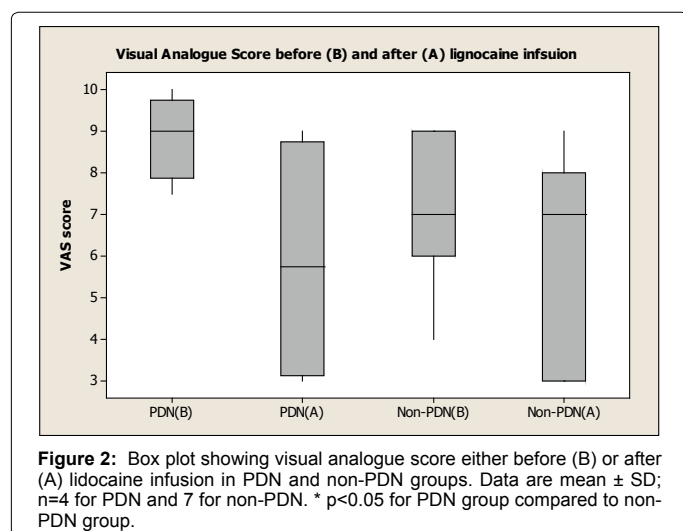
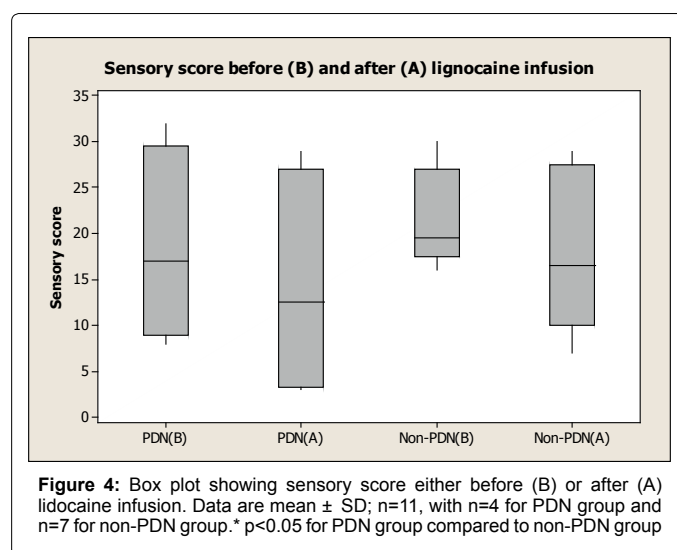
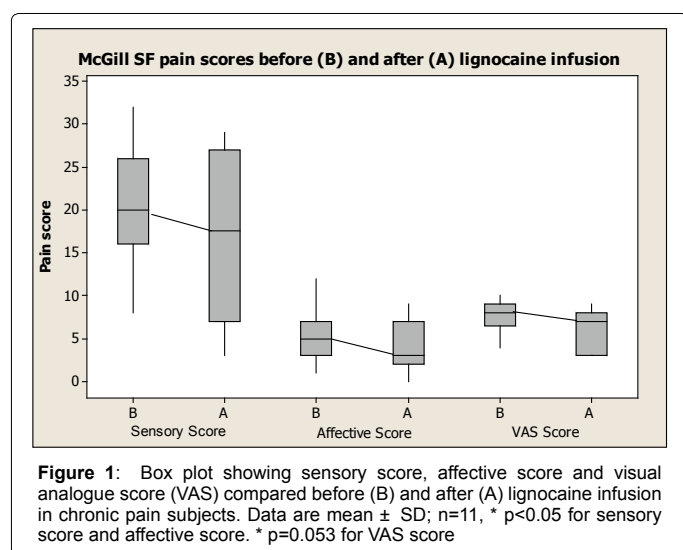
a significant ($p < 0.05$) reduction of affective pain score, 41% after lignocaine infusion in PDN group compared to 21% in non-PDN group (Figure 3). In contrast, the sensory pain score reduction after lignocaine infusion was 23% in PDN group compared to 17% in non-PDN group. These data were statistically not significant ($p > 0.05$) (Figure 4).

All 11 patients had no reported adverse effects and their observations including electrocardiograms, pulse, blood pressure and oxygen saturation were in normal limits throughout the lignocaine infusion. In this and subsequent figures, PDN (B) = Painful diabetic neuropathy group score before lignocaine infusion

PDN (A)=Painful diabetic neuropathy group score after

lignocaine infusion; Non-PDN (B)=Non-painful diabetic neuropathy group score before lignocaine infusion; Non-PDN (A)=Non-painful diabetic neuropathy group score after lignocaine infusion; VAS=Visual analogue score

The box plot analysis in Figure 2 shows the visual analogue score (VAS) which was part of McGill SF pain score either before (A) or after (B) the lignocaine infusion in PDN group and non-PDN group. Before lignocaine infusion, the VAS mean score was 8.87 ± 1.03 SD (median 9.0) compared to VAS mean score after lignocaine infusion which was 5.87 ± 3.06 SD (median 5.75) (33% pain reduction). In Non-PDN group ($n=7$), before lignocaine infusion, the mean VAS score was 7.07 ± 1.7 SD (median 7) compared to VAS mean score of 6.28 ± 2.43 SD (median



7) (11% pain reduction) after lignocaine infusion. The pain reduction of PDN group compared to Non-PDN group was statically significant (p<0.0015).

The box plot analysis in Figure 3 shows the affective score of McGill pain SF score either before (B) or after (A) the lignocaine infusion in PDN group and non-PDN group. The results show that in the PDN group, the affective mean score was 4.25 ± 2.75 SD (median 4.5) before lignocaine infusion compared to affective mean score of 2.50 ± 3.11 SD (median 1.5) (41% pain reduction) after lignocaine infusion. In Non-PDN group (n=7), before lignocaine infusion, the mean affective score was 6.17 ± 3.54 SD (median 4.5) compared to affective mean score 4.83 ± 3.31 SD (median 3.5) (21% pain reduction) after lignocaine infusion was the pain reduction of PDN group compared to Non-PDN group was statistically significant (p<0.0036).

The box plot analysis in Figure 4 shows the sensory score of McGill pain SF score either before (B) or after (A) lignocaine infusion in PDN group and non-PDN group. In PDN group, the sensory mean score was 18.5 ± 10.75 SD (median 17.0) before lignocaine infusion compared to sensory mean score 14.25 ± 12.84 SD (median 12.5) (23% pain reduction) after lignocaine infusion. In Non-PDN group, before lignocaine infusion, the mean sensory score was 21.50 ± 5.36 SD (median 19.5) compared to sensory mean score 17.83 ± 8.73 SD (median 16.5) (17% pain reduction) after lignocaine infusion. The pain reduction of PDN group compared to Non-PDN group was not statically significant (p=0.3769).

The box plot analysis in Figure 5 shows the 95% pain relief after lignocaine infusion in responder (1) and 5% in non-responder (2) of diabetic patients. The pain reduction in responder compare to non-responder was statistically significant (p<0.0001).

In responder group, the duration of diabetes mean score was 15.5 years ± 0.71 SD, HbA1c mean score was 64 mmol/mol ± 15.5 SD and Age means score was 61.5 years ± 24.75 SD compared to 10 years ± 2.83 SD, 66.5 mmol/mol ± 3.5 SD and 56 years ± 5.66 SD in non-responder group respectively. The data for duration of diabetes, HbA1c and Age in responder group compared to non-responder were not statically significant (p<0.116, p<0.84 and p<0.79 respectively).

Discussion

Painful diabetic neuropathy (PDN) is one of the common complications of diabetes mellitus (DM). About 1/3 of all patients with DM suffer from diabetic neuropathic pain [6] and moreover, it has a huge impact on the quality of life (QoL) of the person [8-10]. There are

several trials which have reported some benefit in the improvement of symptoms of PDN with various antidepressants, anticonvulsants, opioid and topical medications [11-27]. The follow up studies reported that only 23% patients had satisfactory improvement of symptoms of PDN after conventional treatment [28,29]. Most of the patients tolerate the residual pain and live with it, however there are reports of severe PDN with constant unrelenting neuropathic pain, disturbance of sleep and even unable to walk due to severity of pain [8-10]. Lignocaine infusion has been used as a treatment when other conventional treatments were not helpful in various chronic challenging painful conditions including chronic pain syndrome [36,37], chronic neuropathic pain [35] including painful diabetic neuropathy [31-33].

The present data have shown reduction in all 3 domains of pain scores of McGill SF pain questionnaire including visual analogue score of 33%, affective scores of 41% and sensory scores of 23% in PDN group after lignocaine infusion compared to 11%, 21% and 17%, respectively in non-PDN group. The data were statistically significant for VAS and affective scores. However, the data were not statistically significant for sensory scores. This could be due to the statistically significant response of lignocaine infusion on sensory scores in both groups of patients (Figure 1).

Comparison with existing data

The data from this study have clearly shown a significant reduction of McGill SF pain scores- affective score and visual analogue score after lignocaine infusion in patients with PDN compares to those patients with chronic pain (non-PDN). These results are consistent with those obtained by Viola et al. [32] and Kastrup et al. [31] who demonstrated significant reduction of both affective scores and visual analogue scores after lignocaine infusion. The present study measured effectiveness of lignocaine infusion as a treatment on PDN patients compared to chronic pain patients with other causes. In contrast, in their studies Viola et al. [32] and Kastrup et al. [31] measured the effectiveness of lignocaine infusion compared with saline infusion in patients with PDN. In our study, the reduction of McGill SF sensory pain score was 23% in PDN group compared to 17% in non-PDN group. Despite of quarter of reduction of sensory pain score in PDN group, the data were not statistically significant. In contrast Viola et al. [32] and Kastrup et al. [31] showed significant reduction of McGill sensory pain score. This discrepancy in the results could be due to the fact that the lignocaine

infusion responded almost to the same level in both PDN and non-PDN groups. Therefore, the comparison difference was not significant. The present study was similar to that of Viola et al study [32] where all the patients participated with intractable pain and who failed to respond to or intolerant to conventional treatment. It is particularly noteworthy, that in this and the studies done by Viola et al study [32] and Kastrup et al. study [31], no participants had any adverse effects with lignocaine infusion of 5 mg/kg bodyweight. This observation clearly suggests that it is quite safe to use this dose of lidocaine to treat PDN. However, there is a report [41] which reported that lignocaine infusion had marked adverse effects resulting in hypotension and arrhythmia. The study is related to fibromyalgia patients and lignocaine infusion was given consecutively for 6 days. Also, the dose was increased incrementally every day to maximum of 5 mg/kg bodyweight plus 150 mg or total maximum 550 mg [41].

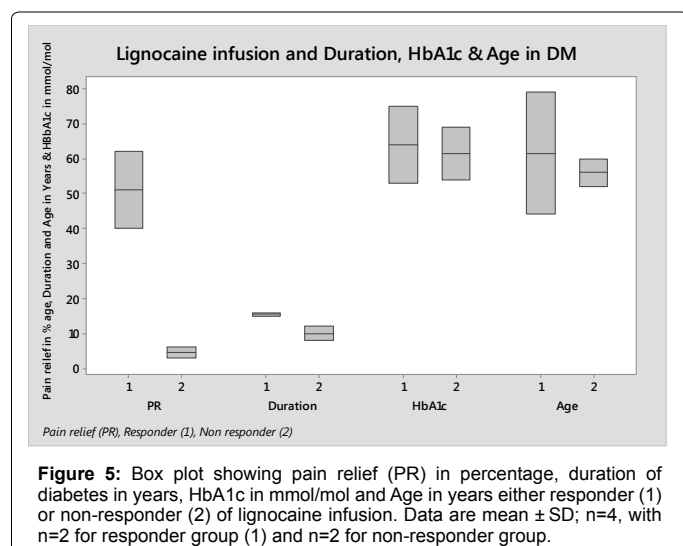
There are several studies reporting significant reduction of pain after lignocaine infusion in PDN and a variety of non-PDN conditions including fibromyalgia [41], headache [42], back pain [43], trigeminal neuralgia [44] and chronic pain syndrome [36,37]. Like previous investigations, the present study also showed a beneficial effect of lignocaine infusion to treat both PDN and non-PDN group. However, in patients with PDN lignocaine infusion was statistically more effective than other causes of chronic pain. PDN pathogenesis involves peripheral and central sensitization with neural plasticity [45]. The half-life of Lignocaine infusion is only 2 hours, however the effect of analgesia reported up to 28 days. This observation suggests that lignocaine infusion may affect not only peripheral, but perhaps central neural plasticity as well. This may be due to the central effect of lignocaine where it was more effective in PDN group.

Strength and Limitation of the study

The study population was well defined for both groups and completed with minimal selection bias as the participations from both PDN and non-PDN groups were referred from Foot Clinic or Pain Clinic for lignocaine infusion, respectively. Moreover, both groups of participants responded 100% in filling McGill SF pain questionnaires. Both groups were similar in age, however all participants in PDN group were males and non-PDN group were females. Recall bias could exist when participants filling out questionnaire. However, most questions from McGill SF questionnaire were based on current or recent physical and mental wellbeing of person, hence recall bias were minimal. The results also show that lignocaine infusion had no significant effect on the ECG, BP, pulse rate or oxygen saturation in the both groups of patients. This was the observational study and all patients were well aware that they were having treatment with lignocaine infusion, therefore possible placebo effect cannot be ruled out. Also the sample size was very small only 4 in PDN group and 7 in non PDN group. Further randomize control trial with large sample needed to see the true results.

Conclusion

Overall, the study has shown that lignocaine infusion is both effective and safe in reducing the chronic intractable pain when conventional treatment are intolerable or not helpful in PDN and non-PDN patients. It is more effective in PDN patients compared to other causes of chronic pain. There is a need for randomize control trial to see the effect of lignocaine infusion especially in PDN. Chronic neuropathic pain including PDN causes modulation of pain at spinal level and plasticity of brain, as a result it's more difficult to treat the refractory pain [45]. Perhaps we may need to consider, lignocaine infusion in early stage when conventional treatments are not helpful.



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