Journal of Anesthesia & Clinical Research

Mogahed et al., J Anesth Clin Res 2017, 8:8
DOI: 10.4172/2155-6148.1000746

Research Article OMICS International

Comparative Study between Intravenous Ketamine and Lidocaine Infusion in Controlling of Refractory Trigeminal Neuralgia

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Received date: June 03, 2017; **Accepted date:** July 27, 2017; **Published date:** July 31, 2017

Abstract

Background: Trigeminal neuralgia (TN) is considered one of the most debilitating disorders. Several medications such as anticonvulsants are available to provide relief from pain. In this study we used either ketamine which acts as an antagonist to N-methyl-d-aspartate receptors, or lidocaine which can block sodium channels in controlling of refractory trigeminal neuralgia.

Aim: The primary outcome of the study was the pain score (The NRS) for pain assessment during the 12-week study period. The secondary outcomes were (1) Amount of analgesic medications (2) Frequency of pain (3) descriptors of pain.

Methods: This study was conducted on 100 adult patients (aged 20-70 years) with refractory trigeminal neuralgia. Patients were enrolled into two groups each group contain 50 patients. In group I (ketamine group), patients underwent ketamine infusion protocol which consisted of 3 sessions of ketamine infusion in a dose of 0.4 mg/Kg over 30-45 minutes in 250 mL of 5% dextrose solution, and each session was performed consecutively every 4 days. In group II (lidocaine group), patients underwent lidocaine infusion protocol which consisted of 3 sessions of lidocaine infusion in a dose of 5 mg/kg over 30-45 minutes in 250 mL of 5% dextrose solution, and each session was performed consecutively every 4 days.

Results: Our results showed that both groups were comparable regarding age, gender and site of pain. A significantly longer duration of pain relief was noticed in group I when compared to group II at 2 weeks, 1 month, 2 months and 3 months (3.11 ± 2.01, 3.15 ± 1.23, 4.23 ± 1.12, 4.50 ± 1.02) $p<0.001$. Immediately after infusion, 12 h and at 24 h pain relief was highly significant decreased in lidocaine group when compared to ketamine group (1.27 ± 1.11, 1.67 ± 1.48, 2.35 ± 1.25) $p<0.001$. At 48 h there was decrease in pain scores in both groups when compared to pre infusion values but without any statistical significance (3.25 ± 1.24, 3.56 ± 1.25) $p=0.216$. The analgesic consumption was significantly decreased in ketamine group. Complications were minor and self-controlled.

Conclusion: The infusion of either ketamine or lidocaine controls pain in refractory trigeminal neuralgia and decreases anticonvulsant consumption with minimal post- infusion complications but with the upper hand to ketamine.

Keywords: Refractory trigeminal neuralgia; Ketamine; Lidocaine; Infusion therapy; Neuropathic pain

Introduction

Trigeminal neuralgia is considered one of the most incapacitating disorders characterized by paroxysms of brief, intense, and stabbing pain affecting one or more divisions of the trigeminal nerve [1]. Treatment guidelines, published from the European Federation of Neurologic Societies, and the American Academy of Neurology, recommend carbamazepine or oxcarbazepine as the first pharmacological choice treatment of TN and baclofen as the second choice. However, some patients may become unresponsive to medication despite of adequate treatment. Also, sometimes, patients cannot tolerate the medications side effects and discontinue, although recommended treatments have achieved sufficient reduction of their pain [2].

Ketamine has an analgesic effect. It exerts its analgesic action both centrally and peripherally at many sites and mediated through multiple receptors. Ketamine also inhibits serotonin and dopamine reuptake and inhibits voltage-gated sodium and potassium channels [3].

Lidocaine has been also used to relieve several types of neuropathic pain, including post herpetic neuralgia [4] and intractable TN [5,6]. This therapeutic effect is due to dose dependent sodium channels block [7,8] both peripherally and centrally [9].

Patients and Methods

This randomization blind study was conducted on 100 adult patients (aged 20-70 years) with intractable trigeminal neuralgia, from the outpatient pain management unit, Tanta University Hospital, after approval of the ethics committee and obtaining verbal and written informed consent from each patient from May 2015 to July 2016. All

patients' data was confidential with secret codes were used for the current study.

Subjects were randomly assigned to treatment sequence *via* a computer-generated randomization list. A randomization list was prepared in sealed envelopes for each patient. Before each procedures, both techniques either ketamine infusion or lidocaine infusion were considered for each patient and patients were received either ketamine (group I) (50 patients) or lidocaine (group II) (50 patients). Numbered and sealed envelopes were placed in the outpatient room and only opened upon the patients' arrival there. Investigator A was responsible for solution preparation according to the randomization list. Investigator B, who was blind to the treatment, was responsible for clinical examination and treatment administration. At the end of each treatment investigator B had to record data and enclose the forms in envelopes that remained closed until the end of the study.

Patients were only included if their mean daily pain intensity was >4 on a 10-point Numercal Rating Scale (NRS) (where 0=no pain and 10=worst pain imaginable) over a period more than one month while on standard treatments which include: physical therapy, pharmacologic therapy with NSAIDs, benzodiazepines, anticonvulsants or antidepressants.

Exclusion criteria were history of drug or alcohol abuse, severe psychiatric disease, previous cardiac arrhythmia, abnormal ECG, angina pectoris, a history of apoplexy, renal impairment, pregnancy, lactation, insufficient pulmonary function or allergy to the study drugs. On the study day, patients were placed in a quiet room and were monitored with a 3-lead ECG, pulse oximeter, and a noninvasive blood pressure (NIBP) monitoring.

A peripheral intravenous line was inserted for fluid and drug administration. Oxygen (4 L/min) was given *via* a nasal cannula and then our patients were included into one of two groups. In group I, ketamine infusion technique, the patients were planned to receive ketamine infusion in a dose of 0.4 mg\Kg over 30-45 minutes in 250 mL of 5% dextrose solution, and this session was performed consecutively every 4 days for 3 sessions. All patients were fasted for 8 h prior to each session. Each session of ketamine infusion was taken at the same time in the day. Midazolam was administered with ketamine in a dose of 2 mg to attenuate the potential central nervous system adverse effects.

Patients were determined to have recovered completely from ketamine infusion if they were fully awake, attained full orientation to time, place, and person, and were not in need of treatment for central nervous system adverse effects. On complete recovery, the patients were discharged from the recovery unit after the end of each session of ketamine infusion with an accompanying reliable person.

In group 2, lidocaine infusion technique, patients underwent lidocaine protocol which consisted of 3 sessions of lidocaine infusion in a dose of 5 mg/kg over 30-45 minutes in 250 mL of 5% dextrose solution, and each session was performed consecutively every 4 days. Patients were fasted for 8 h prior to each session. Each session of lidocaine infusion was taken at the same time in the day for each session.

The primary outcome of the study was the pain score (The NRS) for pain assessment during the 12-week study period. The secondary outcomes were (1) Amount of analgesic medications (2) Frequency of pain (3) descriptors of pain. All were measured at the following periods, just before the initiation of infusion directly after infusion therapy, at 12 h, 24 h, 48 h, 1 week, 2 weeks, 1 month, 2 months, 3 months. Central nervous system adverse effects were assessed with close monitoring of ECG, BP, oxygen saturation, and an open question about discomfort at the end of each session.

Statistical analysis

Sample size calculation was performed before patients' recruitment. Based on a previous reports; 100 patients was calculated for 90% power, α=0.05, β=0.1, using sample size software (G*Power Version 3.00.10, Germany). Descriptive and analytic. The full detailed form is: SPSS 20, IBM, Armonk, NY, United States of America.

Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Independent-samples t-test of significance was used when comparing between two means. Chi-square (χ^2) test of significance was used in order to compare proportions between two qualitative parameters. A one-way analysis of variance (ANOVA) when comparing between more than two means.

Results

Our results showed that both groups were comparable regarding age, gender and site of pain Table 1. A significantly longer duration of pain relief was noticed in group I when compared to group II at 2 weeks, 1 month, 2 months and 3 months (3.11 ± 2.01, 3.15 ± 1.23, 4.23 ± 1.12, 4.50 ± 1.02. p<0.001). Immediately after infusion, 12 h and at 24 h pain relief was highly significant decreased in lidocaine group when compared to ketamine group (1.27 ± 1.11, 1.67 ± 1.48, 2.35 ± 1.25) p<0.001. At 48 h there was decrease in pain scores in both groups when compared to pre infusion values but without any statistical significance in between (3.25 ± 1.24, 3.56 ± 1.25) p=0.216 (Figure 1 and Table 2).

		Group I	Group II	P
Age (Years) (Mean ± SD)		55.21 ± 12.25	60.14 ± 16.21	0.089
Weight (Kg) (Mean ± SD)		60.23 ± 21.22	62.12 ± 11.02	0.577
Sex	**Male (%)**	27 (54)	30 (60)	0.545
	Female (%)	23 (46)	20 (40)	
Location of neuralgia	**1st trigeminal branch (%)**	5 (10)	4 (8)	0.893
	2nd trigeminal branch (%)	20 (40)	22 (44)	
	3rd trigeminal branch (%)	25 (50)	24 (48)	
P value: comparison between G I & G II				

Table 1: Characteristics of the study population.

	Before the initiation of IT	Directly after infusion therapy	12:00	24:00	48:00	1 week	2 weeks	1 month	2 months	3 months
P	0.655	0.001*	0.001*	0.001*	0.216	0.109	0.001*	0.001*	0.001*	0.001*
G I	7.33 ± 1.25	6.92 ± 2.35	6.88 ± 1.12	4.11 ± 1.11	3.25 ± 1.24	3.15 ± 2.0	3.11 ± 2.01	3.15 ± 1.23	4.23 ± 1.12	4.50 ± 1.02
P 1		0.243	0.061	0.001*	0.001*	0.001*	0.001*	0.001*	0.001*	0.001*
G II	7.21 ± 1.42	1.27 ± 1.11	1.67 ± 1.48	2.35 ± 1.25	3.56 ± 1.25	3.75 ± 1.45	6.95 ± 1.33	6.78 ± 1.24	7.11 ± 1.21	7.22 ± 1.28
P 2		0.001*	0.001*	0.001*	0.001*	0.001*	0.347	0.109	0.705	0.971

P value: comparison between GI & GII (T test)

P1: comparison in G I (ANOVA)

P2: comparison in G II (ANOVA)

Table 2: NRS score before and after infusion therapy.

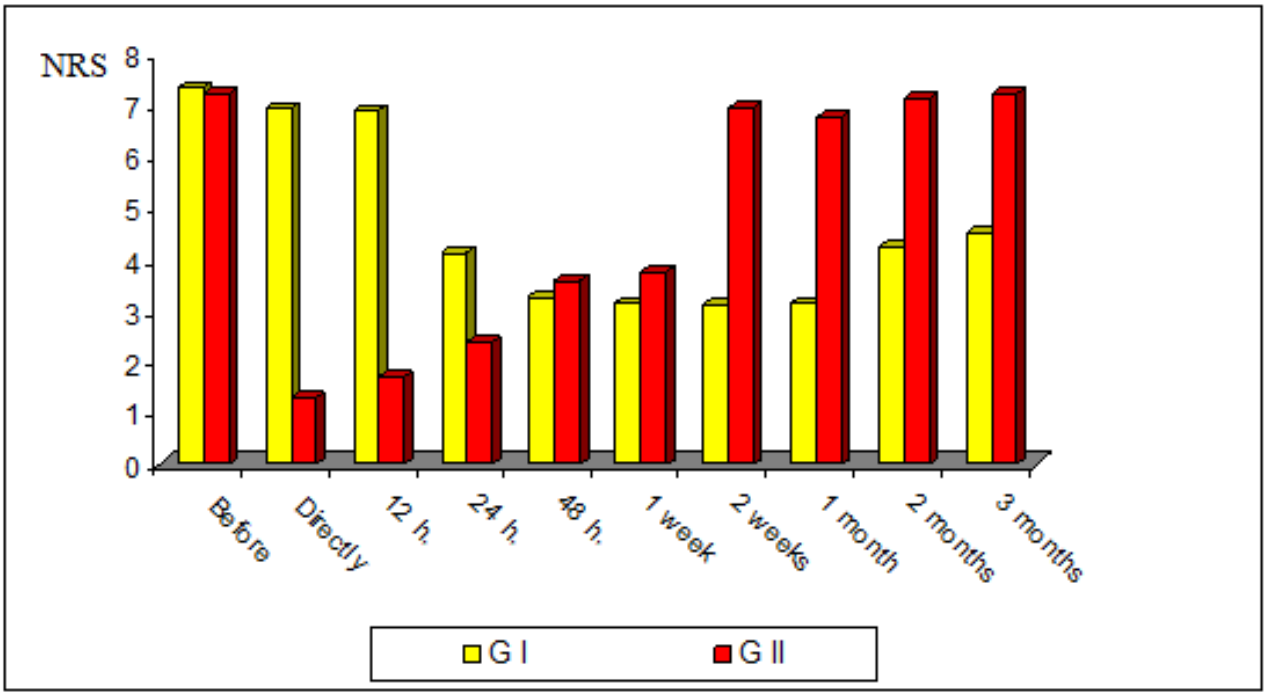

Figure 1: NRS score before and after infusion therapy.

Frequency of pain, allodynia (pain to light touch) pain score and pin prick pain score. Tables 3-5 showed the same pattern with significantly decrease in the number of attacks in lidocaine group immediately after infusion and during 12 h and 24 h follow up period (1.21 ± 0202, 1.56 ± 0.52, 1.23 ± 1.03) $p<0.001$ (Figures 2 and 3). Anticonvulsant therapy (carbamazepine) requirements significantly decreased in lidocaine group immediately after infusion and continued up to one week follow up period $p<0.001$ in ketamine group anticonvulsant therapy started to be significantly decreased at 2 h and continued to be significant during the whole follow up period. When comparing the both groups together, significantly fewer patients used anticonvulsants in ketamine group at 2 weeks, 1 month, 2 months and 3 months. Twelve patients succeeded to stop anticonvulsant therapy in ketamine group during the follow up period, while in lidocaine group nobody succeeded to stop medication Table 6 and Figure 4.

	Before the initiation of IT	Directly after infusion therapy	12:00	24:00	48:00	1 week	2 weeks	1 month	2 months	3 months
P	0.737	0.001*	0.001*	0.001*	0.625	0.209	0.001*	0.001*	0.001*	0.001*
G I	7.12 ± 0.21	4.15 ± 1.2	2.25 ± 1.2	2.0 ± 1.0	2.20 ± 1.01	2.35 ± 1.33	1.21 ± 1.29	1.29 ± 1.31	2.28 ± 1.0	2.42 ± 1.58
P 1		0.001*	0.074	0.001*	0.001*	0.001*	0.001*	0.001*	0.001*	0.001*
G II	7.11 ± 0.01	1.21 ± 0.02	1.56 ± 0.52	1.23 ± 1.03	2.30 ± 1.03	2.65± 1.02	4.27 ± 1.02	4.29 ± 1.11	6.85 ± 1.01	6.94 ± 1.21
P 2		0.001*	0.001*	0.001*	0.001*	0.001*	0.347	0.179	0.072	0.323
P: comparison between GI & GII, P1: comparison in G I, P2: comparison in G II										

Table 3: Frequency of pain.

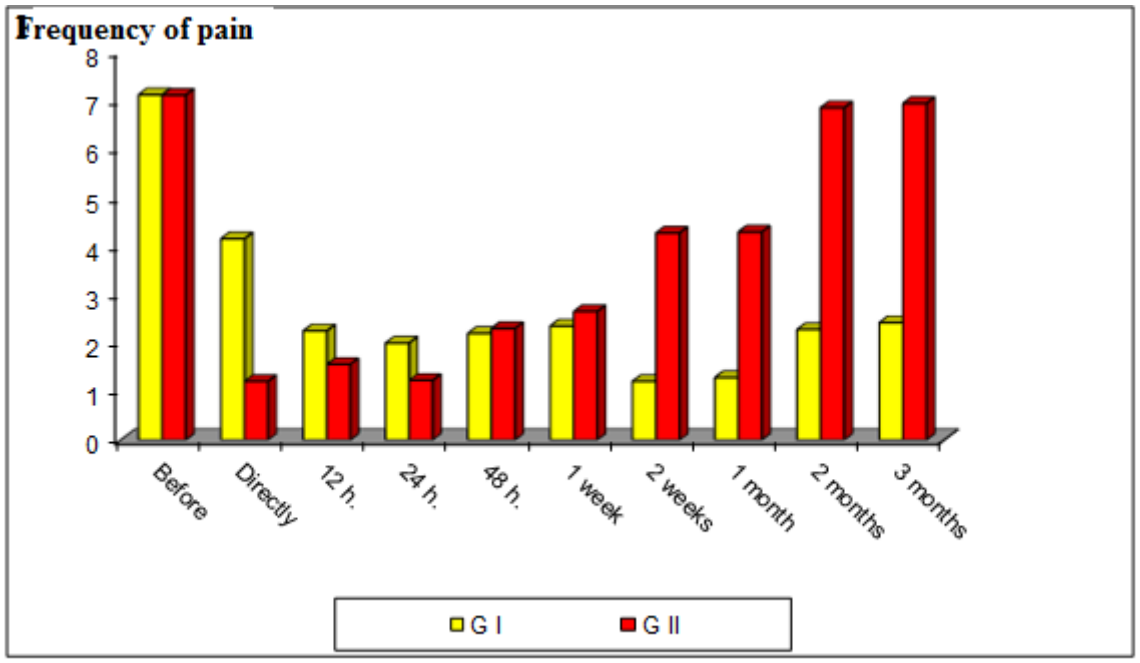

Figure 2: Frequency of pain.

	Before the initiation of IT	Directly after infusion therapy	12:00	24:00	48:00	1 week	2 weeks	1 month	2 months	3 months
P	0.110	0.001*	0.001*	0.001*	0.091	0.086	0.001*	0.001*	0.001*	0.001*
G I	6.58 ± 1.2	6.11 ± 2.0	6.03 ± 2.1	4.10 ± 0.12	3.20 ± 0.23	3.35 ± 1.01	3.10 ± 2.0	3.10 ± 1.0	4.01 ± 1.0	4.44 ± 1.14
P 1		0.157	0.110	0.001*	0.001*	0.001*	0.001*	0.001*	0.001*	0.001*
G II	7.0 ± 1.40	1.16 ± 1.01	1.06 ± 1.01	2.07 ± 1.22	3.50 ± 1.22	3.75 ± 1.28	6.54 ± 1.30	6.60 ± 1.36	7.10 ± 1.06	7.20 ± 1.29
P 2		0.001*	0.001*	0.001*	0.001*	0.001*	0.092	0.150	0.688	0.459

P: comparison between GI & GII, P1: comparison in G I, P2: comparison in G II

Table 4: Allodynia pain NRS score.

	Before the initiation of IT	Directly after infusion therapy	12:00	24:00	48:00	1 week	2 weeks	1 month	2 months	3 months
P	0.993	0.001*	0.001*	0.001*	0.250	0.116	0.001*	0.001*	0.001*	0.001*
G I	7.02 ± 1.0	6.74 ± 2.30	6.64 ± 1.10	4.0 ± 1.10	3.23 ± 1.20	3.10 ± 2.01	3.0 ± 2.02	3.13 ± 1.20	4.20 ± 1.12	4.15 ± 1.0
P 1		0.432	0.074	0.001*	0.001*	0.001*	0.001*	0.001*	0.001*	0.001*
G II	7.01 ± 1.30	1.20 ± 1.10	1.60 ± 1.30	2.30 ± 1.21	3.51 ± 1.22	3.65± 1.41	5.54 ± 1.30	6.67 ± 1.21	7.0 ± 1.32	7.21 ± 1.25
P 2		0.001*	0.001*	0.001*	0.001*	0.001*	0.347	0.179	0.969	0.435

P: comparison between GI & GII, P1: comparison in G I, P2: comparison in G II

Table 5: Pinprick hyperalgesia NRS score.

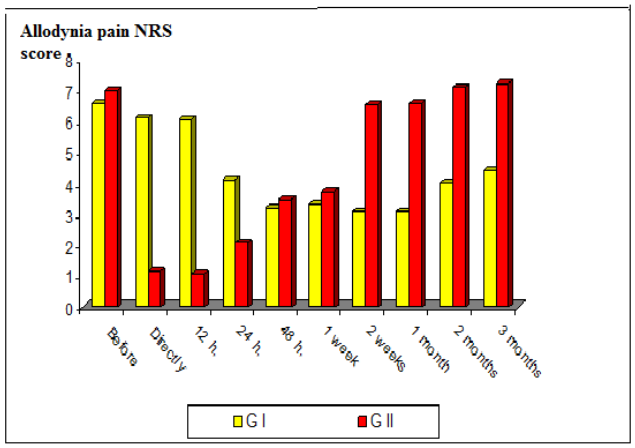

Figure 3: Allodynia pain NRS score.

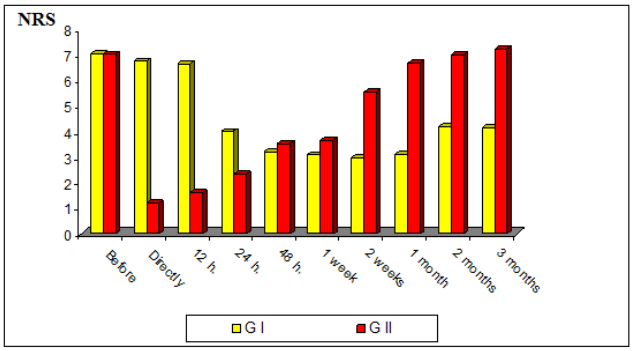

Figure 4: Pinprick hyperalgesia NRS score.

	Before the initiation of IT	Directly after infusion therapy	12:00	24:00	48:00	1 week	2 weeks	1 month	2 months	3 months
P	1.0	0.001*	0.001*	0.001*	0.250	0.606	0.001*	0.001*	0.001*	0.001*
G I	1800 ± 0	658.6 ± 213.65	324.7 ± 195.84	315.6 ± 157.85	337.7 ± 154.36	324.8 ± 145.6	172.6 ± 120.6	162.3 ± 95.68	368.7 ± 84.69	341.5 ± 75.95
P 1		0.432	0.074	0.001*	0.001*	0.001*	0.001*	0.001*	0.001*	0.001*
G II	1800 ± 0	214.6 ± 98.63	203.7 ± 84.65	195.7 ± 79.68	322.5 ± 158.9	310.8 ± 124.7	621.5 ± 214.6	603.9 ± 127.6	1747.8 ± 352.4	1785.9 ± 365.7
P 2		0.001*	0.001*	0.001*	0.629	0.001*	0.347	0.179	0.297	0.773

P: comparison between G I & G II, P1: comparison in G I, P2: comparison in G II

Table 6: Amount of analgesic medications.

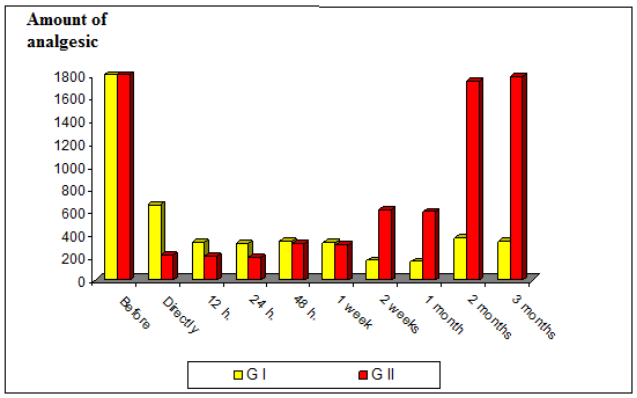

Figure 5: Amount of analgesic medications.

No serious adverse effects were reported during or after the infusion procedure. Number of responders and patient satisfaction were significantly better in group I compared to group II. Ten patients developed adverse effects (Paresthesia, Dysarthria, Dizziness, Headache, Nausea, Blurred vision) in ketamine group versus 6 patients in lidocaine group without any statistical significance p=0.297 (Table 7, 8 and Figure 5).

No. of responders	Group 1	Group 2	X^2	P-value
Responders (%)	26 (52%)	11 (22%)	9.652	0.002*
* =significant				

Table 7: Responders and patient satisfaction No. (%).

Side effects of study drugs	Group 1		Group 2		P-value
	N	%	N	%	
AEs	4	8	8	16	0.218
Tiredness	1	2	2	4	0.558
Feeling drank	1	2	3	6	0.307
Headache	2	4	5	10	0.239
Nausea	3	6	1	2	0.307
Paresthesia	2	4	3	6	0.646
Dry mouth	4	8	2	4	0.399
Fear	1	2	0	0	0.315
Euphoria	1	2	0	0	0.315
Dizziness	5	10	3	6	0.461
Dysarthria	1	2	3	6	0.307

Table 8: Side effects of study drugs.

Discussion

In this study, we compared ketamine infusion versus lidocaine infusion in management of intractable trigeminal neuralgia by 3 consecutive infusion sessions every 4 days. We found that ketamine infusion had a better analgesic outcome for the treatment of neuropathic pain without serious central nervous system adverse effects for up to 3 months, a time which may be adequate to support its long-term effect. The long-lasting effect of ketamine is due to ketamine itself and its metabolite nor ketamine which is produced *via* N-demethylation, resulting in small concentrations of both in blood and tissue [10]. Our study did not include a placebo group because of the ethical dilemma concerning withheld treatment in this population.

Thirty percent were not satisfied with ketamine infusion. A possible explanation may be related to the presence of different pain mechanisms other than NMDA-dependent pathway of ketamine infusion. In randomized clinical trials assessing efficacious medications (eg., antidepressants, gabapentin, and pregabalin) for neuropathic pain, typically <50% of patients experience satisfactory pain relief [11]. It has been suggested that 10-15% of patients with neuropathic pain are really rebellious to all forms of pharmacotherapy [12,13].

The response rate in this study was analyzed by definition of a 50% reduction in NRS score compared with baseline [14], but we think that any reduction of pain compared with baseline might be meaningful to the participants who had been unresponsive to 1800 mg/day oxycarbamazepine (600 mg/8 h) with presence of multiple side effects of tegeratol. In our study 70% of participants in ketamine group had a reduction of >30% of the NRS score, which was similar to that of satisfaction , this percent begin directly after infusion and increase gradually to 40%, 50% and reach about more than 60% during the period of study, this high percent mainly present in the period from 2 days until 1 month, after that the improvement is still present by about more than 50% till the end of the study i.e. 3 months (26 patients developed decrease in pain score >50%).

Also in our study we observed that lidocaine achieved a significant decrease in pain intensity directly after infusion and then increased gradually till 2 weeks, which is considered a long period despite the fact that lidocaine's half-life is 1.6 h [15] (only 11 patients developed decrease in pain score >50%).

Infusion of both anesthetics significantly reduced the pin-prick areas of hyperalgesia and allodynic area as compared with baseline but the analgesic effect of lidocaine was significantly weaker and shorter as compared with ketamine infusion. Ketamine acts as an antihyperalgesic and antiallodynic compound in pain management [16], Patients with TN suffer from allodynia and hyperalgesia is thought to be involved with NMDA receptors [17,18].

The central hyperalgesia, on the other hand, is related to sodium channels located at the ends of mechanoreceptors, in the spinal cord, and in dorsal root ganglia [19]. Boas et al. reported a decrease of central pain with the use of intravenous lidocaine, demonstrating a potential therapeutic value of lidocaine in the treatment of syndromes of intractable neuropathic pain [20]. Lidocaine infusion is an inexpensive and relatively easily administered treatment that has been safely used with very few side effects [21]. The analgesic effects of lidocaine may be observed in patients with diabetic neuropathy, post herpetic neuralgia and in several neuropathic disorders, such as complex regional syndrome type I and II and post-stroke pain [22]. The mechanism of "electric pain" is supposed to be peripheral nociceptor hyper excitability over sodium channels [17,18], and this

descriptor also had a significant response to ketamine infusion but less than lidocaine group. This finding is in accordance with a previous report that suggests that ketamine acts as a pain modulator, targeting sodium channels as well as NMDA receptors [19].

In our study we also observed that frequency of pain is significantly decreased in ketamine infusion group directly after infusion till the end of the study, but in the other group the frequency of pain is significantly decreased mainly in the 1st 48 h and then increase gradually till the end of the study. An experimental study in neuropathic rats showed that intravenous, but not intrathecal or regionally applied, lidocaine yields dose dependent suppression of allodynia associated with nerve injury. Amusingly, the effects last longer than plasma concentrations of lidocaine; however, the mechanism of these prolonged effects remains unknown [23] Similar to this, Attal et al. showed that lidocaine reduced VAS for 6 hrs after the injection and a subgroup of patients experienced prolonged analgesia for up to 7 days in patients with central pain [24]. Furthermore, Arai et al. [25] claimed that in some patients, who suffered from trigeminal neuralgia and had pain relief after receiving lidocaine and magnesium, the therapeutic result continued for nearly one year, which is not the case in our study, this difference is explained by adding magnesium to lidocaine. Although the drug half-life of is only 120 mins, the analgesia provided by systemic lidocaine is prolonged, may be extending over days or even weeks [24]. This may be caused by the action of intravenous lidocaine in the central and peripheral nervous system. Using ketamine for neuropathic pain may be associated with the occurrence of central nervous system adverse effects such as dizziness, dysphoria, and hallucinations [26]. So in the present study, midazolam was administered with ketamine with dose of 1 mg given if there is any adverse effects was present, This might explain why none of the patients in the present study complained of unacceptable adverse effects such as hallucinations or dysphoria.

We chose to use the dose of 5 mg/kg lidocaine over 30 to 45 mins because in this dose lidocaine does not affect the peripheral conduction and acts at hyper excitable neurons without affecting normal nerve conduction, showing good effects on neuropathic pain (Lidocaine between 1.5 and 5.0 mg/kg proved effective dose to suppress ectopic discharge without blocking nerve conduction) [27,28]. As regards safety profiles, intravenous lidocaine and ketamine has been used to relieve several kinds of neuropathic pain without producing major adverse effects [29] similarly, in our study, lidocaine and ketamine infusions caused minor side effects, and during the infusions all the patients were hemodynamically stable with good oxygen saturation.

Conclusion

Ketamine infusion associated with more analgesic effect and lesser anticonvulsant therapy requirementsthan lidocaine infusion in refractory trigeminal neuralgia with minimal post-infusion complications. We think that the short period of follow up is a limitation in our study, however, this is not affecting the validity of our results nevertheless further studies with longer follow up periods may be warranted.

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