COMPARISON OF ANALGESIC EFFICACY OF SYSTEMIC LIGNOCAINE COMBINED WITH DEXAMETHASONE AND LIGNOCAINE INFUSION IN ADVANCE CANCER PATIENTS

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ABSTRACT

Objective: To determine the analgesic efficacy of lignocaine combined with dexamethasone and lignocaine infusion in patients with advance cancer disease.
Study Design: Randomized controlled trial.
Place and Duration of Study: Pain centre Combined Military Hospital Rawalpindi, from Apr 2016 to Nov 2016.
Material and Methods: Total 122 patients, 61 in each group, fulfilling the inclusion criteria were included in this study after approval of the ethical committee. The technique used was non probability consecutive sampling. Two groups were made; group-A received Lignocaine 2mg/kg and group-B Lignocaine 2mg/kg with dexamethasone 0.15mg/kg in continuous infusion over 30 minutes. Both regimen were administered twice weekly for a period of 12 weeks as an outdoor procedure. Numerical rating scale used to measure severity of pain. Baseline and outcome parameters of all patients' i.e. severity of persistent and breakthrough pain and percentage relief of pain were recorded and compared at 12 weeks. Mean ± standard deviations were calculated for quantitative variables, while qualitative variables presented in frequency and percentages. Chi-square test used for qualitative variables while Independent sample t-test used to compare means. A *p*-value <0.05 was considered statistically significant.
Results: When results of group-B compared with group-A, there was a significant reduction in severity of persistent pain from 5.68 ± 2.08 to 2.83 ± 1.01 (*p*-value <0.05), breakthrough pain from 5.90 ± 2.07 to 3.06 ± 1.09 (*p*-value <0.05). The percentage relief of pain was 45.08 ± 15.01 (%) when compared to baseline i.e. 23.35 ± 8.55 (%) (*p*-value <0.05).
Conclusion: Lignocaine with dexamethasone has shown to be effective in reducing complex cancer related pain and disability when compared with Lignocaine alone.

Keywords: Breakthrough pain.

INTRODUCTION

Pain is the most frequent and feared presentation among patients with widespread metastatic advanced cancer. The prevalence of pain in cancer patients ranged from 52% to 77%[1]. According to the recent studies, the prevalence of pain in patients with advanced cancer ranges from 62%-86%[1]. The neurophysiology of cancer pain is complex, as it shares inflammatory, neuropathic, ischemic and compression mechanism[2]. The nature of pain in patients with advanced cancer is nociceptive, neuropathic, visceral and mixed form may also present[2]. Surgery, chemotherapy and radiotherapy are among cancer treatments but these can cause persistent and breakthrough pain in cancer survivors, 50% of them may experience persistent pain and about 40-86% experienced breakthrough pain as reported in various studies[3]. This will adversely affect their quality of life.

Different pharmacological and non pharmacological methods are in practice to get optimum continuous pain relief in patients with complex cancer pain and among them are NSAID's, Opioids, NMDA antagonist, Tricyclic anti depressents, anti convulsants, sodium channel blockers, topical agents, different neuraxial blocks and biopsychosocial interventions[4-5]. To some extent these methods are helpful in treating complex

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cancer pain but the long term consequences of tolerance, dependency, hyperalgesia and sensitization may limit their role as a long term measures.

Lignocaine has been used intravenously since 1960 for several indications, such as regional blocks, antiarrhythmic, as analgesic in neuropathic and central pain, as adjuvant in postoperative pain refractory to opioids[6]. The analgesic action of intravenous lignoicaine reflects the multifactorial aspect of its action, resulting from the interaction with Na-channels and direct or indirect interaction with different receptors and nociceptive transmission pathways. The intravenous dose of lignoicaine should not exceed the toxic plasma concentration of 5µg/mL, and doses below 5mg/kg administered slowly (30 minutes), under monitoring, are considered efficacious and safe[6-7]. The most often prescribed corticosteroid for pain is dexamethasone[8]. Steroids can reduce pain intensity by inhibiting prostaglandin synthesis and reducing tumor vascular permeability[7]. Cancer pain is often under treated due to continuous change in its nature and presence of pain at different anatomical sites[9]. Despite using all the measures, there is dissatisfaction among patients and relatives due to continuous increase in severity of pain and ultimately failure to treat pain. The rationale of this study is to prevent or reduce persistent and breakthrough pain in patients with advanced cancer, which ultimately improve the quality of life and give sense of satisfaction to the dissatisfied patients and relatives.

MATERIAL AND METHODS

This randomized controlled trial was conducted after approval of the ethical review committee of the Hospital, patient's consent and explaining the risks and benefits to the patients. This study was conducted in the department of Pain Medicine, Combined Military Hospital Rawalpindi. The duration of the study was six months, from 01 Apr 2016 to 30 Nov 2016.

The sample size was calculated by using WHO sample size calculator. Keeping level of significance 5% and power 90%, anticipated population proportion 1 (P1) was 52%[1] and population proportion 2 (P2) was 77%[1]. The sample size was 61 in each group. The total sample size of study was 122. The technique used was non probability consecutive sampling.

All the patients who reported to pain clinic with the evidence of complex cancer pain due to advanced metastatic disease and declared non responder to maximum oral or systemic analgesic were included in this study. All the patients with history of heart block, uncontrolled diabetes mellitus, cardiovascular instability, known hypersensitivity to the drugs (Lignocaine and Dexamethasone), hematological malignancy, abnormal cognition, terminally ill patients having life expectancy less than 3 months and the patients on beta blocker were excluded from the study.

Patients were divided in two groups (group-A and group-B) by computer generated method. As per study protocol, all the patients were interviewed, briefed and counseled about the procedure. Pre intervention history, clinical examination and investigations were reviewed and vitals of all the patients were recorded on the proforma and selected for the drug intervention. group-A received Lignocaine infusion 2mg/kg and group-B received Lignocaine 2mg/kg with Dexamethasone 0.15mg/kg in continuous infusion over 30 minutes. During continuous infusion patient vitals were monitored. These infusions were given twice weekly for a period of 12 weeks as an outdoor procedure. In groups, pre and post infusion persistent and breakthrough pain and percentage relief of pain were recorded at baseline and 12 week. Numerical rating scale was used to measure severity of persistent and breakthrough pain. All the parameters related to the severity of pain categorized numerically from 0 to 10 (cm), 0 stands for no pain and 10 for pain as bad as you can imagine, Pain relief parameter was mentioned in percentage, ranges from 0% to 100% (0%=no relief of pain, 100%=complete relief of pain). As per study protocol, average pain in last 24 hrs experienced by the patient recorded as persistent pain, no of episodes of worst pain

experienced in last 24 hr recorded as breakthrough pain, percentage pain relief after intervention recorded in percentage (0 to 100%). In each group, baseline parameters of all patients' i.e age, sex, weight, height, persistent pain, breakthrough pain and percentage relief of pain were compared with outcome parameters at 12 weeks. Data was analyzed with the help of statistical software SPSS Version 20. Mean and standard deviation were calculated for quantitative variables, while qualitative variables were presented in frequency and percentages. Chi square test was used for qualitative variables while Independent samples t-test was used to compare means. A *p*-value of less than or equal to 0.05 was considered statistically significant.

RESULTS

Total 122 patients were included in the study, divided into two groups. Both groups had 61 patients in each. Mean age in group-A and group-B were 59.80 ± 5.07 and 59.24 ± 5.90 years respectively (*p*=0.58). Weights of the patients were also not statistically significant between two groups. Majority of the patients were male (59%) in group-A and were female (54.1%) in group-B respectively as shown in table-I.

As per study results, in group-A (Lignocaine alone) there were reduction in parameters when compared baseline with 12 weeks as, Persistent pain reduced from 5.59 ± 2.45 to 4.81 ± 1.96 (*p*-value=0.05), and breakthrough pain from 7.04 ± 2.25 to 6.90 ± 1.85 (*p*-value 0.71). The percentage relief of pain was 20.77 ± 6.13 when compared at baseline 18.4 ± 7.57 % i.e. (*p*-value 0.06). All the parameters except persistent pain were showed statistically insignificant results as *p*-value >0.05 shown in table-II.

Similarly, in group-B (Lignocaine + dexamethasone infusion) there were reduction in parameters when compared baseline with 12 weeks as, persistent pain reduced from persistent pain form 5.26 ± 1.83 to 3.01 ± 0.76 (*p*-value<0.05), breakthrough pain from 5.90 ± 2.07 to 3.06 ± 1.09 (*p*-value <0.05). The percentage relief was 45.08 ± 15.01 when compared to baseline i.e. 23.35 ± 8.55 (*p*-value <0.05). All the parameters showed statistically significance results i.e. (*p*-value <0.05) as shown in table-III.

Table-I: Patients Demographic Data.

Patient Parameters	Group A	Group B	*p*-value
Age	59.80 ± 5.07	59.24 ± 5.90	0.58
Sex	Male/Female (36/25) N=61	Male/Female 28/33(N=61)	0.30
Weight	58.86 ± 6.0	60.27 ± 7.24	0.24

Table-II: Group A (Lignocaine Infusion).

Outcome Parameters	Baseline Values	Values at 12 weeks	*p*-value
Persistent Pain (NRS)	5.59 ± 2.45	4.81 ± 1.96	0.05
Breakthrough Pain (NRS)	7.04 ± 2.25	6.90 ± 1.85	0.71
% Relief of Pain	18.4 ± 7.57	20.77 ± 6.13	0.06

Table-III: Group B (Lignocaine + Dexamethasone Infusion).

Outcome Parameters	Baseline Values	Values at 12 Weeks	*p*-value
Persistent Pain (NRS)	5.26 ± 1.83	3.01 ± 0.76	<0.001
Breakthrough Pain (NRS)	5.90 ± 2.07	3.06 ± 1.09	<0.001
% Relief of pain	23.35 ± 8.55	45.08 ± 15.01	<0.001

DISCUSSION

The analgesic efficacy of intravenous Lignocaine was first reported in cancer and post-operative patients[7]. Moreover, Lignocaine shown

to provide analgesia by blocking both peripheral and central voltage-dependent sodium channels. It can also relieve both deafferentation and central pain[7]. Steroids are among the most commonly used medications in palliative care. A Canadian study of ambulatory palliative care, patients with cancer demonstrated that 40% of patients were receiving corticosteroids and dexamethasone was the medication most commonly added by palliative care specialists[8]. Previously, various randomized controlled trials (RCTs) have already assessed the efficacy of IV Lignocaine and dexamethasone in non-cancer and cancer related neuropathic pain such as diabetic neuropathy, postherpetic neuralgia, spinal cord injury, peripheral nerve injury, post-amputation pain, sciatica, and neuralgia[9-15]. As per author knowledge, it is the first comparative prospective study of its own kind in which analgesic efficacy of two different regimens; Lignocaine combined with dexamethasone and Lignocaine alone were compared in patients with advance cancer disease and still no randomized study has determined the analgesic efficacy of Lignocaine with dexamethasone infusion.

In this study, we evaluated the analgesic efficacy of Lignocaine with dexamethasone and Lignocaine infusion. In literature; different doses of Lignocaine have been tried but lignoicaine toxicity is more likely to manifest when its plasma concentration reaches 5µg/mL[16]. Doses between 1mg and 2mg/kg administered as continuous infusion of 1.5mg/kg/h, which correspond to plasma concentrations of 2µg/ml are considered small[17]. The toxic dose seems to change in patients with terminal diseases[18]. The intravenous administration of low doses of Lignocaine was effective in the management of chronic pain refractory to conventional oral treatment[18].

In our study, Lignocaine infusion group showed reduction in all parameters from baseline when compared at 12 weeks but the results were statistically insignificant except there was a significant reduction in persistent pain. In Lignocaine with dexamethasone infusion group, there was reduction in all parameters when compared to baseline. There was statistically significantly decrease in severity of persistent and breakthrough pain. The incidence of breakthrough pain and percentage relief of pain was also improved in this group.

In a study done by Peixoto RD, Hawley P, signified that intravenous lignoicaine infusion 5mg/kg has been clearly demonstrated as effective for pain relief. In this study a total of 122 lignoicaine infusions were administered in 51 cancer patients. Twenty-five (49%) had a major response, 12 (23.5%) had a minor response, and 14 (27.5%) were considered nonresponders.[19] Lignoicaine infusion is a useful option to consider when other pain treatments have not been successful[19]. Sharma, Rajagopal, Palat, Singh, Haji, Jain, conducted a study in which eligible patients received both Lignocaine and placebo infusions separated by two weeks. Primary endpoints were magnitude and duration of pain relief. Fifty patients were included in the study. Pain relief was significantly better (p<0.001) and more patients reported a decrease in analgesic requirements (p=0.0012) after lignoicaine infusion than after placebo. Onset of analgesia was noted at a mean of 40 ± 16.28 minutes after initiation of infusion of IV lignoicaine. Mean duration of this analgesia, 9.34 ± 2.58 days after the single infusion, was significantly longer than that for placebo (p<0.01)[20]. Hanks *et al*. observed that dexamethasone showed tendency for better results than prednisolone in patients with pain due to compression of the nerve. A total of 16 out of 34 patients responded to the treatment: 8 (38%) out of 21 patients treated with prednisolone and 8 (62%) out of 13 patients treated with dexamethasone. However, this trend could have been associated with relatively higher doses of dexamethasone (4mg daily, n=7; 8mg, n=4, 16mg, n=2) compared with the doses of prednisolone (30mg daily, n=10; 20mg or less, n=11)[21]. As per results, Lignocaine infusion with dexamethasone showed statistically significant reduction in severity of persistent and breakthrough pain. There was reduction in incidence of breakthrough

pain and ultimately decreased in rescue analgesic required to treat that pain. The percentage relief of pain was 45.08 ± 15.01 when compared to baseline i.e. 13.35 ± 8.55 (p-value<0.05).

Although intravenous Lignocaine has been used to relieve several kinds of chronic pain but combining Lignocaine with dexamethasone the results are very promising as shown in results. Keeping in mind the results, its safety profile at this dose, intravenous lignoicaine with dexamethasone has been used effectively to relieve cancer related pain without producing major adverse effects. Similarly, in our study, the infusions caused minor side effects and during the infusions all the patients remained haemodynamically stable. Moreover, no major complications were observed. Finally, our results should be interpreted with some caution given the fact that the drugs follow up and effects were studied till 12 weeks and the author did not follow the drug effects and outcome parameters after 12 weeks. Although intravenous Lignocaine with dexamethasone is not a first line treatment but when first line medications fail to help, pain specialists may try it as an add-on treatment.

CONCLUSION

Lignocaine with dexamethasone has been shown to be effective in reducing cancer related pain, disability and rescue analgesia requirement when compared with Lignocaine alone.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Van den Beuken-van Everdingen M, de Rijke J, Kessels A, Schouten H, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: A systematic review of the past 40 years. Annals of Oncology 2007; 18(9): 1437-49.
2. Raphael J, Ahmedzai S, Hester J, Urch C, Barrie J, Williams J, et al. Cancer Pain Part 1 Pathophysiology; Oncological, Pharmacological, and Psychological Treatments: A perspective from the british pain society endorsed by the UK association of pallia-tive medicine and the royal college of general practitioners. Pain Medicine 2010; 11(5): 742-64.
3. Mishra S, Bhatnagar S, Chaudhary P, Rana S. Breakthrough cancer pain: Review of prevalence, characteristics and management. Indian J Palliat Care 2009; 15(1): 1-4.
4. Gregory H. Pharo, DO, Linqui Zhou. Pharmacologic management of cancer pain. The Journal of the American Osteopathic Association 2005; 105: 21-8.
5. Lynette A, Menefee Pujol, Daniel A, Monti. Managing cancer pain with nonpharmacologic and complementary therapies. J Am Osteopath Assoc 2007; 10(7): 15-21.
6. Lauretti G. Mechanisms of analgesia of intravenous lignoicaine . Revista Brasileira de Anestesiologia 2008; 58(3): 280-86.
7. Golzari S, Soleimanpour H, Mahmoodpoor A, Safari S, Ala A. Lignoicaine and Pain Management in the Emergency Department: A Review Article. Anesth Pain Med 2014; 4(1): e15444.
8. Melissa Vyvey Steroids as pain relief adjuvants Can Fam Physician 2010; 56(12): 1295-97.
9. Viola V, Newnham H, Simpson R. Treatment of intractable painful diabetic neuropathy with intravenous Lignocaine. J Diabetes Complicat 2006; 20(1): 34-9.
10. Baranowski A, De Courcey J, Bonello E. A trial of intravenous lignoicaine on the pain and allodynia of postherpetic neuralgia. J Pain Symptom Manage 1999; 17(6): 429-33.
11. Finnerup N, Biering-S Rensen F, Johannesen I, Terkelsen A, Juhl G, Kristensen A et al. Intravenous Lignoicaine Relieves Spinal Cord Injury Pain. Anesthesiology 2005; 102(5): 1023-30.
12. Attal N, Rouaud J, Brasseur L, Chauvin M, Bouhassira D. Systemic lignoicaine in pain due to peripheral nerve injury and predictors of response. Neurology 2004; 62(2): 218-25.
13. Wu C, Tella P, Staats P, Vaslav R, Kazim D, Wesselmann U et al. Analgesic Effects of Intravenous Lignoicaine and Morphine on Postamputation Pain. Anesthesiology 2002; 96(4): 841-48.
14. Medrik-Goldberg T, Lifschitz D, Pud D, Adler R, Eisenberg E. Intravenous lignoicaine, amantadine, and placebo in the treatment of sciatica: A double-blind, randomized, controlled study. Reg Anesth Pain Med 1999; 24: 534–40.
15. Marchettini P, Lacerenza M, Marangoni C, Pellegata G, Sotgiu M. Lignoicaine test in neuralgia. Pain 1992; 48(3): 377-82.
16. Sucena M, Cachapuz I, Lombardia E. Plasma concentration of lignoicaine during bronchoscopy. Rev Port Pneumol 2004; 10: 287-96.
17. Abelson KS, Hoglund AU Intravenously administered lignoicaine in therapeutic doses increases the intraspinal release of acetylcholine in rats. Neurosci Lett 2002; 317: 93-6.
18. Tei Y, Morita T, Shishido H. Lignoicaine intoxication at very small doses in terminally ill cancer patients. J Pain Symptom Manage 2005; 30: 6-7.
19. Peixoto R, Hawley P. Intravenous Lignoicaine for cancer pain without electrocardiographic monitoring: A retrospective review. J Palliat Med 2015; 18(4): 373-77.
20. Sharma S, Rajagopal M, Palat G, Singh C, Haji A, Jain D. A Phase II Pilot Study to evaluate use of intravenous lignoicaine for opioid-refractory pain in cancer patients. J Pain Symptom Manag 2009; 37(1): 85-93.
21. Hanks G, Trueman T, Twycross R. Corticosteroids in terminal cancer-a prospective analysis of current practice. Postgrad Med J 1983; 59(697): 702-06.