

PAIN RELIEF IN NEUROPATHIC PAIN-A COMPARISON BETWEEN 0.5% BUPIVACAINE AND 0.5% BUPIVACAINE STREPTOMYCIN COMBINATION

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ABSTRACT

Objective: To compare the effectiveness of a combination of streptomycin and bupivacaine for the management of neuropathic pain against bupivacaine alone.

Study Design: A randomized controlled double blinded trial.

Place and Duration of Study: Pain clinic Combined Military Hospital (CMH) Rawalpindi, CMH Nowshera, Dermatology Dept. Military Hospital (MH) Rawalpindi, Department of Medicine, Surgery CMH Nowshera Feb 2009 to Feb 2010.

Material and Methods: Fifty patients with post herpetic neuralgia (PHN), 10 patients with trigeminal neuralgia and 20 patients with nerve entrapment pain were included in the study. For each type of neuropathic pain, the patients were randomly divided into two groups. Group (B) received nerve blocks using 0.5% bupivacaine and group (BS) received nerve blocks using 0.5% bupivacaine and streptomycin 1gm combination. A series of four nerve blocks on alternate days were given. VAS (Visual Analogue Scale) was recorded at four, eight and twelve weeks after the last nerve block. Mean baseline VAS and at 12 weeks post treatment in groups B and BS were compared for pain relief and the mean VAS at 12 week post treatment in both the groups was compared for the difference in pain relief between the two groups. Students't test was used for statistical analysis utilizing SPSS 10 versions.

Results: Post herpetic neuralgia - group (B): at 12 weeks, mean VAS was 5.75 in gp (B) and 2.26 in gp (BS) respectively. Nerve entrapment pain- group (B): at 12 weeks, mean VAS was 6.62 whereas in group (BS) VAS was 1.33. Trigeminal neuralgia-group (B) At 12 weeks mean VAS was 7.0. gp (BS) mean VAS was 1. Pain relief achieved was excellent.

Conclusion: Streptomycin and bupivacaine combination is an effective modality to manage neuropathic pain. The pain relief achieved by streptomycin-bupivacaine combination is superior to that achieved with bupivacaine alone.

Keywords: Neuropathic pain, Post herpetic neuralgia, Streptomycin-bupivacaine, Trigeminal neuralgia.

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INTRODUCTION

Neuropathic pain is a chronic form of pain in which there is functional abnormality of the nervous system. Normal non-noxious stimuli can at times be interpreted as painful by the abnormal nervous system, while at other times, pain may be perceived in the absence of any direct stimulus. There are many types of neuropathic pains e.g post herpetic neuralgia (PHN), trigeminal neuralgia, post diabetic neuralgia (PDN), post traumatic neuralgia (PTN), scar pain, nerve entrapment syndromes, complex regional pain syndrome (CRPS I, II),

stump pain, etc. Post herpetic neuralgia (PHN) is characterized by ongoing pain and varying degrees of sensory deficits, allodynia, and hyperalgesia. Multiple symptoms (and mechanisms) may be present at the same time in neuropathic pain with features that change over time¹.

The therapy can be tailored according to the underlying mechanisms². The out break of herpes zoster may damage the peripheral nerve apparatus from the dorsal root to cutaneous nerve endings. Surviving but damaged cutaneous nociceptors in the area of pain may have abnormal spontaneous activity and be sensitized to mechanical or other stimuli³. These changes may in part be due to accumulation of sodium channels at sites of injury, the target of local anesthetics⁴. Similiar patho-physiological

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changes have been seen in trigeminal neuralgia and nerve entrapment pain. Bupivacaine is an aminoamide local anesthetic. It potently blocks Na⁺ channels in neuronal membranes and

Aminoglycosides act at phosphatidylinositol receptor in the neuronal membrane and compete with Ca²⁺ at this site thereby inhibiting the transduction of pain⁹.

Table-1: Post Herpetic Neuralgia Group-I: Bupivacaine (B) Bupivacaine/streptomycin (BS) Comparison Paired Samples Test

	Paired differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Pair 1 VASBup PHN4wks- VASBupstrept4wks	1.5789	1.4070	.3228	.9008	2.2571	4.892	18	.000
Pair 2 VASBup PHN8wks- VASBupstrept8wks	2.9474	1.4230	.3255	2.2612	3.6332	9.028	18	.000
Pair 3 VASBup PHN12wks- VASBupstrept12wks	3.4737	1.3892	.3187	2.8041	4.1432	10.900	18	.000

Table-2: Nerve Entrapment Painbupivacaine (B) - Bupivacaine/Streptomycin (BS) comparison Paired Samples Test

	Paired differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Pair 1 VAS 4wks (B) Gp-VAS 4weeks (BS) Gp	2.5000	1.1952	.4226	1.5008	3.4992	5.916	7	.001
Pair 2 VAS 8wks (B) Gp-VAS 8weeks (BS) Gp	4.2500	1.1650	.4119	3.2461	5.2239	10.319	7	.000
Pair 3 VAS 12wks(B)Gp-VAS 12weeks (BS) Gp	5.5000	1.1952	.4226	4.5008	6.4992	13.015	7	.000

The value of 'p' was less than 0.0001.

inhibits spontaneous discharges in damaged neurons which play a key role in the pathogenesis of neuropathic pain. Local anesthetics may interact with many membrane phospholipids and proteins and thereby affect a variety of cellular activities. Local anesthetics can affect several subtypes of kinases as protein kinase C (PKC)⁵, guanosine triphosphate-binding proteins (G proteins)⁶ and many of the various receptors that activate them⁷.

Bupivacaine inhibits pERK (extracellular signal-regulated kinases (ERK 1 and 2) activation resulting from different modes of Ca²⁺ influx through the plasma membrane and thereby inhibits neuropathic pain⁸.

Amino glycosides including streptomycin have been found to cause modulation of the release of excitatory neurotransmitters from primary afferent nerve terminals.

Aminoglycosides have therefore been studied as possible agents in the management of neuropathic pain¹⁰. Streptomycin suppresses autotomy behavior in rats and reduces autonomy scores when applied locally¹¹.

To study the synergistic effects of bupivacaine and streptomycin for the management of neuropathic pain, a double blind randomized controlled trial was carried out.

MATERIAL AND METHODS

This was a randomized controlled double blind trial carried out at the pain clinic Combined Military Hospital (CMH) Rawalpindi and CMH Nowshera from Feb 2009 to Feb 2010. After approval of the hospital ethical committee, 50 patients with post herpetic neuralgia (PHN), 10 patients with

trigeminal neuralgia and 20 patients with nerve entrapment pain were included in the study.

Students "t" test was used for analysis utilizing SPSS version 10.

Table-3: Paired Samples Test.

	Paired Differences					t	df	Sig.(2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Pair 1 vasBup 4wks-vas Bu-SGP 4wks	2.7500	2.6300	1.3150	-1.4348	6.9348	2.091	3	.128
Pair 2 vasBup 8wks - vas Bu-SGP 8wks	4.5000	1.7321	.8660	1.7439	7.2561	5.196	3	.014
Pair 3 vasBup 12wk -vas Bu-SGP 12wks	5.5000	1.0000	.5000	3.9088	7.0912	11.000	3	.002

Table-4: Response to treatment (12 weeks).

	Pre treatment VAS	Inj.0.5% Bupivacain	Inj. Streptomycin and Bupivacaine (BS) VAS
Post herpetic neuralgia	7055 (0.51 SD)	5.75 (0.71SD)	2.26 (0.933 SD)
Trigeminal Neuralgia	9.200 (1.412SD)	7.00 (0.707)	1.7(0.500)
Nerve entrapment pain	8.37(0.916)	6.62(0.749)	1.33(1.00)

All values are mean with + S.D.

All patients of either gender above 18 years of age were included in the study. Patients who had known allergy to streptomycin or infection at the injection site or hepatic or renal impairment were excluded from the study. For each type of neuropathic pain, the patients were randomly divided into two groups. Group (B) received nerve blocks using 0.5% bupivacaine and group (BS) received nerve blocks using 0.5% bupivacaine and streptomycin 1gm combination. The operator was blinded to the drug used. The pain relief and side effects were recorded by an experienced pain clinician also blinded to the drug used. The pain relief was recorded at four, eight and twelve weeks after the last nerve block. Visual analog scale (VAS) was used as a pain measurement tool. VAS was recorded at the start of treatment and at different time intervals. The mean VAS at the start of treatment (baseline) was compared with the VAS at twelve week in group (B) and (BS) and then the VAS after treatment at twelve weeks between the two groups was compared and the statistical analysis was carried out for the difference in means and the value of " p".

Study Drugs, Dosage

Streptomycin sulphate 1 gm was dissolved in 4ml of 0.5% bupivacaine plain which was available in 10 ml ampoules marketed as ABBOCAINE. For PHN, intercostal nerve blocks were given. For trigeminal neuralgia, supra orbital, infra orbital, maxillary and mandibular nerves were blocked. For nerve entrapment pain, the nerve within the scar was blocked.

Pain Relief Rating: Pain relief after the treatment was graded in the following manner:-

- Excellent = Mean VAS 0 To 2.5
- Good = Mean VAS 2.5 To 5.0
- Fair = Mean VAS 5.0 To 7.5
- Poor = Mean VAS more than 7.5

RESULTS

Group-1: Post Herpetic Neuralgia Bupivacaine(B): Number of patients completing the study were 20 (n=20). Male to female ratio was 3:1 and the mean age was 61.90 years (11.11 SD). Mean duration of pain was 7 months. Pre treatment VAS was 7.55 (0.51 SD). Twelve weeks after the last block, mean

VAS was 5.75 (0.71SD). The pain relief achieved was fair only.

Post herpetic Neuralgia Streptomycin Bupivacaine Combination (BS): Nineteen patients completed the study and six patients were lost in the follow up.

Out of 19 patients, there were 13 males and six females. Mean age was 60.52 years. Pre treatment VAS was 8.00 (0.66SD). There was not much difference in the mean age and pre treatment VAS in both groups. Twelve weeks after inj. Streptomycin + bupivacaine the mean VAS was 2.26 (0.933). The pain relief achieved was excellent.

Group-II: Nerve Entrapment Pain Bupivacaine(B): Nine patients completed the study and one patient was lost in the follow up. There were four male and five female patients. Mean age was 39.5 years (12.87 SD). Pre treatment VAS was 8.37 (0.916SD). Twelve weeks after 0.5% bupivacaine nerve block the mean VAS was 6.62 (0.744 SD). The pain relief achieved was fair only.

Group-II: Nerve Entrapment Pain Bupivacaine/Streptomycin(BS): Nine patients completed the study and one patient was lost in the follow up. Among these nine patients the male to female ratio was 2:1 and the mean age was 43 years (8.27SD). Pre-treatment VAS was 8.88 (0.92 SD). Twelve weeks after 0.5% bupivacaine/Strept nerve block the mean VAS came down to 1.33 (1.00 SD).

The pain relief achieved was excellent.

Group--III: Trigeminal Neuralgia-Bupivacaine Alone (B): All five patients completed the study. Among this group the male to female ratio was 2:3 and the mean age was 59 years (15.313 SD). Pre treatment mean VAS was 9.2 (0.836 SD). Mean VAS after 12 weeks of last nerve block with bupivacaine alone was 7.0 (0.707 SD). The pain relief obtained was fair to poor.

Group-III: Trigeminal Neuralgia Bupivacaine/Streptomycin (BS): Four patients completed the study and one patient was lost in the follow up.

There was equal number of male and female patients in this group. The mean age

was 49.25 years (22.66 SD) and the mean duration of pain was 10.75 months. Pretreatment (Baseline) VAS was 8.00 (1.41 SD). Twelve weeks after 0.5% bupivacaine /streptomycin (BS) treatment, the mean VAS came down to 1.75 (0.500 SD).

Pain relief achieved after 12 weeks of bupivacaine /streptomycin (BS) treatment was "Excellent".

Group-III: Trigeminal Neuralgia Bupivacaine (B) Bupivacaine/Streptomycin (BS) Comparison: Paired sample t the value of "p" was 0.002

DISCUSSION

Pain caused by a lesion of the peripheral or central nervous system is commonly termed neuropathic pain, and this type of pain frequently persists, even following normal repair of the injured tissue¹². In a clinically significant proportion of cases, the neuropathic pain becomes chronic, severely debilitating, and extremely difficult to treat. PHN is characterized by ongoing pain and varying degrees of sensory deficits, allodynia, and hyperalgesia. Once postherpetic neuralgia is well established, it is likely that tissue inflammation is no longer present but abnormal activity in damaged or primary afferents may still produce neurogenic inflammation by release of substance P and other peptides into the skin. The peptides might further sensitize primary afferents by evoking the local synthesis of prostaglandins. The vicious cycle can continue indefinitely because of on going abnormal activity in the damaged nerve¹³.

Similarly in tissue trauma or surgery, release of other mediators of pain like 5HT, along with substance P may sensitize primary afferent neurons causing pain in cases of nerve entrapment pain or scar pain. In trigeminal neuralgia, hyper excitability of primary afferent neurons has been reported in several different trigeminal nerve injury and inflammation animal models, including chronic constriction nerve injury (CCI), axotomy, and inflammatory models¹⁴.

The major cellular mechanisms of neuropathic pain include ectopic or

spontaneous nerve activity and peripheral and central hyper excitability, phenotypic changes in pain conducting pathways, secondary neurodegeneration, and morphological reorganization¹⁵. Hyperexcitability in small and large peripheral sensory nerves acts as an important driving mechanism for neuropathic pain and can account for the initiation and maintenance of central hyperexcitability. Thus, block of local excitability using the local anaesthetic, lidocaine, reverses primary and secondary allodynia in neuropathic pain¹⁶.

Bupivacaine inhibits the spontaneous ectopic activity in damaged sensory neurons by its action on Na⁺ channels in the cell membrane¹⁷. It also inhibits substance P binding to neuronal membranes and inhibits the transmission of pain. Furthermore bupivacaine inhibits the substance P induced long lasting facilitation of nociceptive transmission in the dorsal horns¹⁸.

Autotomy has been proposed as an experimental model for neuralgia pain. Stajic¹⁹ showed that topically applied streptomycin significantly reduced the autotomy phenomenon after sciatic nerve section in rats.

Considering these synergistic actions, streptomycin was combined with lidocaine 2% for the management of various neuropathic conditions²⁰⁻²². In our study we combined bupivacaine with streptomycin in place of lidocaine due to its long duration of action and excellent sensory blocking profile.

In our previous study (1996)²³, we selected 20 patients suffering from post herpetic neuralgia, trigeminal neuralgia and nerve entrapment pain. The over all pain relief in the three groups was 60% (good to excellent), 25% (fair), 15% (no significant relief). The 60% pain relief experienced by the patients in this study was comparable to the study conducted by F. Gallagher and Colleagues²¹ in which the success rate was 50%. The study conducted by Salim²² for the management of post herpetic neuralgia with streptomycin lidocaine 2% combination also showed 44% patients finding complete pain relief after three injections and 64% finding the pain relief very helpful.

Some other studies have been carried out, (Khurram et al²⁴ achieving about 80% pain relief in PHN using streptomycin- lignocaine 2% combination.

The short comings of the previous studies included small number of patients, lack of control and non uniform pain assessment ratings. Khurram et al²⁴ used injections and intercostal nerve blocks with placebo which is not very kind to the chronic sufferers of pain. They actually used saline as placebo for the intercostals nerve blocks which is not placebo but algogenic.

Although our previous study for the role of streptomycin bupivacaine combination²³ showed good to excellent pain relief in some neuropathic conditions, but it was not case controlled.

In the present study, since the controls were employed in each type of neuropathic pain studied, the extent of pain relief achieved with streptomycin-bupivacaine combination was more distinct and significant as compared to bupivacaine alone. Using bupivacaine in the control group also provided some pain relief in the control group which was about 20-30% (fair). The pain relief in trigeminal neuralgia group was 90% (Excellent) which was comparable to the pain relief in a similar study by Bibhukalyani Paset al²⁴. The pain relief in the post herpetic neuralgia group was 71.75% and was comparable to Salim²². The pain relief in the nerve entrapment group was 86.77% and the scores on the visual analog scale (VAS) were significantly lower at three months as compared to the baseline values or the control group. There were no significant side effects or signs of streptomycin toxicity.

CONCLUSION

Streptomycin and bupivacaine combination is an effective modality to manage neuropathic pain. The pain relief achieved by streptomycin – bupivacaine combination is superior to that achieved with bupivacaine alone. Further studies may explore the synergistic actions of streptomycin and bupivacaine combination for managing

different pain mechanisms in a single neuropathic condition.

CONFLICT OF INTEREST

This study has no conflict of interest to declare. Abstract and results of this study were accepted and presented in an oral presentation at the International conference on Medical Education, organised by Association for Excellence in Medical Education (AEME) and held on 7th-9th March 2014 at University of Health Sciences (UHS) Lahore, Pakistan. No funding was received from any agency or institution.

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