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Research Article

A COMPARISON BETWEEN INTRAMUSCULAR ADENOSYLCOBALAMIN AND ORAL MECOBALAMIN IN THE TREATMENT OF HERPETIC NEURALGIA

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ABSTRACT

Background: Herpes zoster is as a result of the reactivation of the varicella zoster virus that lies dormant in the dorsal root ganglia after a chicken pox infection. When the immunity is weakened, the virus resurface later resulting in the distinct lesion of herpes zoster - grouped vesicles on an erythematous base. However the most appalling, common and persistent of the symptoms of herpes zoster (HZ) is the associated neuralgia which if left untreated may progress into a more notorious form – post herpetic neuralgia (PHN) that persists for months and up to years after the rash has healed. Research results after studies on the more significant among intramuscular adenosylcobalamin (IM.AdCbl) and oral mecobalamin (O.MeCbl) in the treatment of herpetic neuralgia (HN) has been inconsistent.

Objectives: The study that follows analyses the analgesic effect of IM.AdCbl and O.MeCbl and the time taken for both these drugs to reduce the intensity of pain in subjects of all age groups and those over 50 years of age. The study also looks into the adverse effects of these drugs.

Subjects and design: This is a prospective randomised study which included 96 patients in two groups – treatment group (n=58) and control group (n=38) and a subgroup of 66 patients who were over 50 years in two groups treatment group (n=44) and control group (n=22).

Method: The treatment group was administered IM.AdCbl at 1mg per day for 4 weeks and the control group was given with O.MeCbl at a dose of 1500 micrograms in three divided doses per day for 4 weeks. Pain intensity was assessed using the visual analogue scale before treatment, 1 week after treatment and on week

4. The adverse effects were noted down.

Result: Although both drugs showed a similar end results (0.64±0.552 and 0.42±0.599) on week 4, MeCbl taken orally dropped the intensity of pain experienced by the subjects drastically 1 week after treatment began. The results were consistent on patients over 50 years of age as well. IM.AdCbl showed relatively more adverse effects compared to O.MeCbl in both groups of subjects.

Conclusion: O.MeCbl gives better relief to patients after 1 week of treatment. O.MeCbl has the added advantage of having fewer adverse effects, being non-invasive and requiring lesser clinical output and can thus be considered the better of the two drugs.

Keywords: Herpes Zoster, Herpetic neuralgia, Adenosylcobalamin, Mecobalamin

INTRODUCTION

HZ is an acute infectious viral disease characterised by vesicular eruptions of the skin or mucous membrane along a distinct dermatome. However the most appalling of its symptoms is often the extreme pain that may be burning, stabbing and often incapacitating in nature owing to the inflammation of dorsal root ganglia or extramedullary cranial nerve ganglia [1]. HZ is caused by reactivation of the varicella zoster virus (VZV) in the dorsal root ganglion and is linked in part to the progressive decline of cell-mediated immunity with age [2]. HZ presents as grouped vesicles on an erythematous base lasting for 2–3 week accompanied by moderate to severe pain that may not resolve for weeks to months or even years after the lesions have subsided [3]. HN is the pain that occurs within 30 days of the onset of the rash and PHN is the **pain that lasts for more than 6 months** after the rashes have healed [4,5]. Since HZ is most often presented as linear unilateral rashes that wrap around the body like a girdle, it is known as 'shingles' derived from the Latin word cingulum, for 'girdle' in lay terms [6].

HN is a prodromal pain that increases rapidly in intensity and diminishes slowly and may include different symptoms like itching, burning and tickling besides the intense pain [7]. The intensity of pain can deteriorate the quality of life in patients with HZ as the pain may disrupt everyday physical and social functions of cases often not even premising them adequate sleep [8]. Age and a decrease in cell mediated immunity reactivates the virus causing an inflammation of the peripheral nerve and the skin damage resulting from it causes the acute pain [9]. This leads to associated tissue inflammation and destruction that instigates the release of inflammatory mediators that further activate peripheral nociceptors directly by lowering the threshold of nociceptors. This causes an ongoing discharge and hyper excitability which ultimately triggers the peripheral sensitization [10]. Prolonged nociceptor discharge enhances the response of dorsal horn neurons to afferent stimuli and expands its receptive field, accounting for central sensitization, which leads to spontaneous pain and allodynia without a marked sensory loss.

HN is treated using analgesics like NSAIDS and opioids, anti-epileptics, phototherapy, corticosteroids, antihistamines and neurotrophic agents like cobalamins. In recent years cobalamins have niched a significant role in the management of pain associated with HZ as they help regenerate peripheral nerves, promote the myelination and transport of the axonal cytoskeleton and can help maintain the proper functioning of the nervous system [11]. Cobalamins have known to have pain reduction properties and had initially been categorised as an analgesic and not an essential nutrient until the recent past. Researches show that Cobalamins have beneficial effects on clinical and experimental peripheral neuropathy. AdCbl is used in the treatment of nutritional deficiencies, neurological disorders and for pain management while MeCbl significantly reduce continuous pain, paroxysmal pain, and allodynia in the subacute herpetic neuralgia patients [12]. The following study compares two forms of cobalamins – AdCbl and MeCbl in their efficacy in treating HN.

PATIENTS AND METHODS

Objective:

The purpose of this study is to compare between O.MeCbl and IM.AdCbl in the treatment of HN. Both, the degree of analgesic effect of the two drugs and the time taken for the analgesic effect to set in has been researched on. The better of the two drugs can thus be chosen in the treatment of not just HN but neurological pain in general, neurological disorders and nutritional deficiency of cobalamins.

Study Design:

The study was conducted between September 2016 and February 2018 and in order to minimise or eliminate bias of any kind, randomization was adhered to. Every subject was as likely as the others to be assigned to the treatment (or control) group. All non-immunocompromised HZ patients over the age of 18 were included in the studies. Patients presenting with PHN, those with a prior history of HZ, those with an active malignancy and drug or alcohol abusers were excluded from the study. Patients were randomised into 2 groups. The treatment group was administered 1mg IM.AdCbl per day and the control group was given 1500 mcg O.MeCbl per day and the intensity of pain the subjects perceived was measured using visual analogue scale. Table 1 presents the study design comprehensibly.

Treatment group	Control group
58 cases	38 cases
IM.AdCbl	O.MeCbl
1mg/day for 4 weeks	1500 micrograms/day for 4 weeks
VAS score on the first day of admission, 1, week after treatment and on week 4	VAS score on the first day of admission, 1, week after treatment and on week 4

Table 1: Study design

Method and Measurement:

The treatment group was administered IM.AdCbl at a dose of 1 mg/day for 4 weeks and the control group was given O.MeCbl at a dose of 1500 micrograms for the same period. The primary outcome measures were the overall pain assessed using the Visual Analogue Scale before treatment, 1 week after treatment and on week 4 after treatment had begun. Visual analogue scale is a 100-millimeter (mm) horizontal line labelled "no pain" at one end and "worst pain imaginable" on the other end. It is an easy to use main measurement instrument with the help of which patients can easily pinpoint the intensity of pain they are going through [13]. Patients were asked to mark the intensity of the pain experienced on this line. The score on visual analogue scale correlates well with acute pain levels, although it has an error of about 20mm [14]. Scoring on the Visual analogue scale was done without bias and with ease as the patients were asked to pinpoint the intensity of pain they percieved on a scale from 0 to 10 where 0 is no pain at all and 10 worst pain ever. Adverse effects if any, were looked for and noted down. The number of days it took for the progression of the erythema into vesicles, vesicles into crusts and crusts to heal away was also closely observed and jotted down.

RESULT

A total of 96 patients with HN who met the inclusion criteria and participated in the study were assesed in this study, out of which 58 were in the treatment group treated with IM.AdCbl and 38 were in control group treated with O.MeCbl. All patients were followed up for one month. The mean age of the patients in the treatment group and control group were 58.16±14.305 years and 53.13±15.543 years respectively. Table 2 shows that the distribution of patients of different age groups in both the groups was similar. (*P* value was more than 0.05)

Drug	N	Age	Statistical value	P value
IM. AdCbl	58	58.16±14.305	t=1.626	0.107
O.MeCbl	38	53.13±15.543	t=1.598	0.114

Table 2: A comparison between age and groups

P value <0.05 is significant

Drug	M	F	Total	P value
IM. AdCbl	26	32	58	
O.MeCbl	14	24	38	0.527
Total	40	56	96	

Table 3: A comparison between sex and groups

P value <0.05 is significant

Drug sex cross tabulation shows that there was no statistically significant difference in the gender distribution between the two groups. ($\chi 2$=0.602, *P*=0.527>0.05). There was thus a similar group of patients belonging to either sex in both the groups.

VAS scores were assessed on before the treatment began, 1 week after treatment began and on the 4th week of treatment. There was no significant statistical difference between the VAS score of the patients on either groups before the treatment began. However, after 1 week of treatment, the VAS score of O.MeCbl group was significantly lower than that of the IM.AdCbl group (t=3.770, p=0.000<0.01), and the difference was statistically significant. Yet again, after four weeks of treatment, there was no significant difference (t=1.820, p=0.072) between the O.MeCbl group and IM.AdCbl group.

Group	N	VAS1	VAS 2	VAS4
IM.AdCbl	58	4.14±1.206	2.16±0.834*	0.64±0.552
O.MeCbl	38	3.71±1.088	1.34±1.146	0.42±0.599

Table 4: A comparison between VAS1 and VAS2 in the two groups

* t=3.7770, P=0.000<0.001 on treatment after 1 week

Both IM.AdCbl and O.MeCbl has similar and significant end result with regards to reducing the intensity of pain experienced in HN. However, O.MeCbl efficiently brought down the pain experienced one

week after treatment began compared to IM.AdCbl.

Group	N	Pain	Rash	Nausea	Diarrhoea	Total	%
IM.AdCbl	58	58	1	3	1	63	109
O.MeCbl	38	0	3	5	2	10	26

Table 5: A comparison between adverse effects in the two groups

Patients in the control group experienced 83% fewer adverse effects when compared to those in the treatment group. All 58 subjects in the treatment group reported of pain. However there was no injection site reaction seen in any patients treated with IM.AdCbl. The commonest adverse effect reported by those in the control group was nausea. Other adverse effects seen were mild rashes and diarrhoea.

Since HZ is caused by the reactivation of the VZV owing to depreciation of immunity, it is in most part, a disease of the elderly and the immunocompromised. The analyses was repeated on a subgroup of subjects in the data pool to include only patients over 50 years of age. There was a total of 66 patients of age over 50 years and the mean age of patients was 64.41±9.184 years and 63.00±9.933 years in the IM. AdCbl and O.MeCbl groups respectively.

Group	N	Age	Statistical value	P value
IM. AdCbl	44	64.41±9.184	t=0.572	0.569
O.MeCbl	22	63.00±9.933	t=0.557	0.581

Table 6: A comparison between age and groups

P value <0.05 is significant

Drug	M	F	Total	P value
IM. AdCbl	19	25	44	0.527
O.MeCbl	8	14	22	
Total	27	39	66	

Table 7: A comparison between sex and groups

P value <0.05 is significant

There was no statistically significant difference between the two groups with regards to age implying that there was similar distribution of patients of different age groups in the treatment and control group. As we can seee from Table 7, there was a total of 27 male and 39 female subjects in the study. Drug sex cross tabulation showed that the groups were also similar in term of gender distribution (*P* value >0.05).

Group	N	VAS1	VAS2	VAS4
IM.AdCbl	44	4.37±1.155	2.30±0.701*	0.73±0.544
O.MeCbl	22	3.68±0.945	1.59±1.141	0.59±0.666

Table 8: A comparison between VAS1 and VAS4 in the two groups

*t=3.7770, *P*=0.000<0.01 on treatment after 1 week

Patients over 50 years of age showed almost superimposing results when compared to all the subjects in the study. The VAS score on treatment after 1 week was statistically significant favouring O.MeCbl over IM.AdCbl (P=0.00<0.01). There was no statistically significant difference in the VAS scores of subjects before the treatment and on the 4th weeks after treatment.

Group	N	Pain	Rash	Nausea	Diarrhoea	Total	%
IM.AdCbl	44	44	1	2	0	47	107
O.MeCbl	22	0	2	3	2	7	32

Table 9: A comparison between adverse effects in the two groups

Subjects in the control group experienced 75% fewer adverse effects compared to those in the treatment group. The commonest adverse effect reported by the elderly under O.MeCbl was nausea while pain was the most reported adverse effect by the elderly under IM.AdCbl.

DISCUSSION

Of all the presenting symptoms of HZ, HN is infamous for being the most challenging to manage, especially if left untreated in the acute stage which is why early intervention is crucial [15]. It is essential to manage HN not only for relief from acute pain, but also since there is evidence of severe HN leading to PHN. 67.34% of all the subjects in my studies were over the age of 50. This is consistent with findings in literature that there is a sharp rise in the risk of contracting HZ after the age of Fifty [16]. Analogues of Vit B12 – AdCbl and MeCbl have been used as analgesics for several decades. AdCbl, is routinely administered intramuscularly at a dose of 1mg per day in the treatment of diabetic neuropathies, nutritional deficiencies and neurological

disorders whereas the ectopic spontaneous neuronal discharges that initiate spontaneous pain, hyperalgesia, and allodynia can be suppressed by MeCbl [17]. My research on 98 subjects concluded that patients under O.MeCbl experienced a drastic drop in the pain percieved one week after treatment with fewer adverse effects when compared to those treated with IM.AdCbl. So with this result, it can be taken into account that for all the above mentioned conditions O.MeCbl is be a better alternative. The possibility of taking an oral preparation will also allow anonymity and patient preferences to be taken into account when deciding on the kind of treatment to be prescribed.

It is also in best interest to treat patients presenting with HZ a few days into the onset of symptoms, patients with comorbidities and immunocompromised patients with O.MeCbl in order to reduce their intensity of pain and to curb the progression of acute herpetic neuralgia into the more notorious PHN. The administration of O.MeCbl has shown to have a better effect initially although it gives the same end result as an IM.AdCbl. Since O.MeCbl is more convenient to use when compared to IM.AdCbl and has lesser adverse effects, it can be used with ease in the treatment of conditions such as nutritional deficiencies, management of pain and neurological disorders as well.

CONCLUSION

The study proves that the analgesic efficacy of O.MeCbl at a dose of 1500 micrograms per day in three divided dose is superior to that of IM.AdCbl at a dose of 1mg per day one week after treatment begins as the pain intensity of subjects under O.MeCbl dropped drastically 1 week after treatment began, when compared to those under IM.AdCbl. However, both the drugs tend to have similar end results. The results appeared to be the same for patients over 50 years of age as well. Compared to IM.AdCbl, O.MeCbl had 83% and 75% fewer side effects among all age groups and among the elderly respectively. O.MeCbl has the added advantage of being more convenient, show fewer adverse effects, non-invasive and involving lesser clinical input and can thus be considered the better of the two drugs.

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