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Is the use of Methylcobalamin alone or in combination with Lidocaine clinically more effective than Lidocaine alone in relieving Herpes Zoster related neuropathic pain with subcutaneous injections?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not Methylcobalamin alone or in combination with Lidocaine is clinically more effective than Lidocaine alone in relieving Herpes Zoster related neuropathic pain with subcutaneous injections.

STUDY DESIGN: This is a systematic review of three peer-reviewed primary studies. All were randomized, controlled trials published between the years of 2014 and 2016.

DATA SOURCES: Data sources obtained for this review were published in peer reviewed journals and selected from PubMed Database.

OUTCOME MEASURED: The outcomes measured reflected the effectiveness of incorporating subcutaneous Methylcobalamin in the treatment regimen for neuropathic pain in Herpes Zoster patients. The patients in each study reported their pain at baseline and after treatment using an 11-point NRS to assess a significant change in pain.

RESULTS: All three studies conducted showed significant improvement in Herpes Zoster related neuropathic pain for the participants whose treatment regimen included subcutaneous Methylcobalamin injections.

CONCLUSIONS: The evidence presented in this review is conclusive that the use of subcutaneous injections of Methylcobalamin in the treatment of Herpes Zoster related neuropathic pain is significantly more effective than Lidocaine alone.

KEY WORDS: Methylcobalamin, Lidocaine, Herpes Zoster, neuropathic pain

INTRODUCTION

Herpes Zoster (HZ), commonly known as Shingles, is a condition caused by the reactivation of the latent varicella zoster virus (VZV). The virus initially causes the condition known as Chicken Pox and lies dormant in the dorsal root ganglia after recovery. With viral reactivation, HZ is characterized by vesicles, pruritis, and neuropathic pain in a unilateral dermatomal distribution of the affected nerve.^{1,2,3} The disease generally lasts between 7-10 days, while the skin may take 2-4 weeks to return to normal. The most common complication of HZ is postherpetic neuralgia (PHN), pain that persists after the rash has subsided. Although reactivation is usually benign in children, the pain can be debilitating when HZ presents in adults.⁴ Most patients who experience PHN will have resolution within a few weeks or months. However, some people will have pain that persists for years with significant interference with their daily life.⁵

In order to prevent HZ and the associated PHN complications, the VZ vaccine was released for use in the United States in 1995. However, prior to the vaccine availability, almost all persons were susceptible to infection of VZV. According to the CDC, thirty percent of the current US population will have a reactivation of VZV in their lifetime, leading to significant morbidity annually. Incidence rates have shown to increase with age, the highest being in the sixth decade and beyond. Though uncommon to have more than one episode, recurring reactivations of VZV have been correlated with immunocompromised states, such as individuals with AIDs or certain cancers like leukemia.^{4,5,6}

It is estimated that the United States has one million HZ cases annually. Though a majority of these patients can be followed and treated through routine outpatient visits, according to the Center of Disease Control and Prevention (CDC), one to four percent of these HZ patients

are hospitalized due to complications. Approximately thirty percent of those hospitalized are immunocompromised. According to a recent study reported by the CDC, HZ is the underlying cause of 96 deaths on average each year.⁵ In 2004, the United States' economic burden of HZ related healthcare was estimated to be \$1.9 billion annually.⁸ With routine varicella immunizations, administration of prophylaxis, and action in removing susceptible personnel from possible exposures, national costs involved with postherpetic complications have and will continue to be cut down.⁷

Although specific populations such as the elderly and immunocompromised are known to be at a higher risk for developing HZ, the exact cause of the reactivation of VZV is unknown.⁵ Therefore, it is pertinent to find the most effective treatment for HZ and its complications. To shorten the length and lessen the severity of the illness, antiviral therapy including acyclovir, valacyclovir, and famciclovir are available. Therapy should be administered as soon as possible after the rash has appeared. In order to prevent secondary infection, antibiotics can be given. Symptomatic relief can be managed with analgesics, wet compresses, or calamine lotion. Neuropathic pain treatment currently includes local lidocaine, anticonvulsants, TCAs, and cryotherapy.⁶

As the risk of HZ increases with age, the risk of developing neuropathic pain increases as well, experienced by 10-30% of these patients.⁵ Although the symptoms usually resolve within weeks to months, the pain can last up to years in select patients. Due to the severe interference with daily life, it should be evaluated if there are more effective treatments to prevent the painful complications of HZ. Clinical use of Methylcobalamin (MeB₁₂) therapy has shown to improve symptoms of peripheral neuropathy and autonomic dysfunction.¹ It is proposed that including

local injections of Methylcobalamin into the treatment regimen of PHN could improve the HZ patients' neurological response.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not Methylcobalamin alone or in combination with Lidocaine is clinically more effective than Lidocaine alone in relieving HZ related neuropathic pain with subcutaneous injections.

METHODS

The studies utilized in this systematic review included three randomized controlled studies. The populations were comprised of patients with HZ related neuropathic pain, including acute herpetic neuralgia (AHN) and acute ophthalmic herpetic neuralgia (AOHN). The studies evaluated the use of subcutaneous (SC) injection of MeB12 in the treatment regimen to improve neuropathic pain of the populations. The intervention used in the first study was SC injection MeB12 alone¹ while the other two studies' intervention was SC MeB12 combined with SC Lidocaine.^{2,3} These populations were compared to controlled groups given SC injection of Lidocaine alone¹ and SC injection of Lidocaine plus IM injection of MeB12.^{2,3} The demographics and characteristics of the studies are shown in Table 1.

The keywords "herpes zoster" or "shingles", "lidocaine", and "vitamin" were searched to locate sources from PubMed Database. The articles were chosen based off of relevance to the clinical question and included outcomes that were patient oriented (POEMS). Inclusion criteria required studies that were RCTs or other primary research studies and studies that were published after 2007. Exclusion criteria included studies using populations with neuropathic pain not related to HZ or medication interventions administered by a route other than SC injections. All articles were published in English, in peer-reviewed journals, between the years 2014-2016.

The statistics reported included Relative Benefit Increase (RBI), Absolute Benefit Increase (ABI), Number Needed to Treat (NNT), and 95% Confidence Interval (CI).

Table 1: Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Xu ¹ , 2014	Single center, RCT	40	>25	Herpes Zoster dx lasting 20-180 days. Experienced cutaneous or/and subcutaneous itch and/or pain in the skin.	U/L itch for < 20 days or outside vesicular region. Any significant medical condition. Hypersensitivity to thiamine or cobalamin. Use of supplement with vitamin B. Cognitive impairment. Topical analgesics or nerve blocker use < 10 days before the baseline.	5	MeB12 1000 µg VS. 1.0% Lidocaine 30mg/3.0mL - SC daily in morning, 6 days/week for 4 weeks
Xu ² , 2016	Single center, observer-blind, RCT	49	>50	AOHN 4-7 days after onset of vesicles with pain, >5 lesions, and swelling. Worse pain score ≥ 6 in past 24 hrs. U/L rash on forehead, vertex, eyebrow, side of nose, or regions adjacent.	U/L pain in vesicular region > 7 days after rash onset. Pain outside the V1 regions. Any significant medical condition. Cognitive impairment.	1	SC combo of MeB12 1000 µg and 20 mg lidocaine (2.0 mL) VS. IM MeB12 plus SC lidocaine - daily in morning, 6 days/week for 2 weeks
Xu ³ , 2016	Single center, observer-blind, RCT	89	>50	AHN 4-7 days after onset of vesicles with pain and > 25 lesions. Worst pain score ≥ 6 in past 24 hrs. U/L rash within T5-10 dermatome.	U/L pain in vesicular region > 7 days after rash onset. Pain outside the target regions. Steroid, analgesics, or capsaicin use within 4 weeks of study entry. Any significant medical condition. Cognitive impairment.	3	SC combo of MeB12 1000 µg and 20 mg lidocaine (2.0 mL) VS. IM MeB12 plus SC lidocaine - daily in morning, 6 days/week for 2 weeks

OUTCOMES MESURED

Outcomes measured were those of patient-oriented evidence that matters (POEMS). Each study used an 11-point numeric rating scale (NRS) (0 = pain, 10 = most painful sensation imaginable) to measure the level of neuropathic pain per the patient. The NRS was used at baseline and at the end of treatment to measure the extent of pain relief with intervention. Xu¹ baseline was the worst pain over the past 24 hours on the day previous to treatment. Xu² and Xu³

baseline was the worst pain since rash onset. Xu¹ endpoint was the worst pain over the past 24 hours on day 28 of treatment. Xu² and Xu³ endpoint was the worst pain during the past 24 hours on day 14 of treatment.

RESULTS

This review analyzed three randomized controlled studies to assess if the use of SC MeB12 would improve relief of HZ related neuropathic pain as compared to SC Lidocaine alone. Each study compared a treatment regimen that included SC MeB12 to a controlled treatment regimen with only SC Lidocaine. All three studies used dichotomous data.

In the study conducted by Xu et al,¹ 92 participants were assessed for eligibility. Inclusion criteria were as follows: a confirmed diagnosis of HZ lasting ≥ 20 days, age > 25 years, having pain/itch in the area associated with the HZ rash, and a worst itch NRS score of ≥ 4 in the past 24 hours.¹ This study was looking at relief of itch symptoms as well as pain. Postherpetic itch is not effected by increased age like PHN is, therefore, this study included younger participants than other studies observing only PHN. Exclusion criteria were as follows: HZ rash lasting < 20 days, neuropathic itch outside the target regions, any clinically significant medical condition or severe general disease, cognitive impairment, hypersensitivity to cobalamin, use of vitamin B-containing supplements, and use of topical analgesics or nerve blockers in target region within 10 days before the baseline visit.¹ The final two exclusion criteria were mentioned to prevent alteration of reported pain scores. The exclusion of those with HZ < 20 days was to prevent the healing or the loss of scabs altering the sensations (itch and pain) measured.

After removing participants that did not meet criteria, declined to participate, or other reasons, 80 participants were left to be randomized by computer generation and distributed into 4 groups. For the purpose of this review, only two groups, B₁₂ ($n = 20$) and LD ($n = 20$) were

observed. The B₁₂ group received SC injections of MeB₁₂, while the LD group received SC 1.0% lidocaine injections, into the regions of crusted lesions where the patients experienced itching and pain. Frequency of dosing was once daily every morning, 6 times per week for 4 weeks. The patients were observed for the following hour and discharged without symptoms of discomfort. The patients' NRS pain score was measured from baseline to days 7, 14, and 28 of treatment.¹ For the purpose of this review, only baseline and day 28 were observed, assessing for improvement to a pain score ≤ 3 .

Compliance was measure by the treating physician by recording the number of treatment sessions attended by each patient and the number of missed or canceled appointments. Three patients were discontinued by the investigator for noncompliance. Two others dropped out due to lack of improvement and rapid pain quenched. A total of 5 out of 40 participants (2 of group B₁₂ and 3 of group LD) dropped out of this study.¹

At baseline, the control and intervention groups had similar mean pain scores. Group B₁₂ had a mean pain score of 6.65, while group LD had a mean pain score of 6.60. After a treatment period of 28 days, 65% of group B₁₂ reported an improved pain score ≤ 3 . In contrast, 0% of group LD reported a pain score ≤ 3 .¹ By calculating the NNT to be 2 patients, these results are significant. It can be concluded that local MeB₁₂ injection provided a significant reduction in HZ neuropathic pain compared to local 1% lidocaine injection.

Table 2: Pain NRS score at baseline and endpoint of intervention and control group, Xu¹

Xu ¹	Mean pain NRS at Baseline	% of Pts with pain NRS ≤ 3 at 28-Day Endpoint	RBI	ABI	NNT
Intervention: SC B ₁₂	6.65 (SD 0.88)	0.65	1.00	6.5	2 patients (CI n/a)
Control: SC Lido	6.60 (SD 1.35)	0.0			

In the study conducted by Xu et al,² 106 participants were assessed for eligibility. Inclusion criteria were as follows: AOHN ≤ 7 days after rash onset, >5 lesions on rash, aged >50 years, severe pain in the region associated with the HZ rash, a worse pain score ≥ 6 in the previous 24 hours, and willingness to comply with the allocated treatment and follow-up measurements. This study included participants at an older age than Xu¹ because HZ neuropathic pain increases significantly with age. Exclusion criteria were as following: pain > 7 days after rash onset, neuropathic or significant pain outside the V1 regions, any clinically significant medical condition or laboratory abnormality, and cognitive impairment.²

After meeting criteria, 98 participants enrolled in the study and were randomized by computer generation and distributed into control and intervention groups. Those were separated out into 4 total groups based on rash onset, a control and intervention group with onset ≤ 3 days and a control and intervention group with onset between 4-7 days. For the purpose of this review, only the latter two groups were observed, B₀ ($n = 25$) and B₁ ($n = 24$). The B₀ control group received IM MeB12 and SC lidocaine injections, while the B₁ intervention group received a combination SC injection of MeB12 and lidocaine, into the subcutaneous regions of the affected V1 innervations where the patients experienced pain. Frequency of dosing was once daily every morning, 6 times per week for 2 weeks. The patients were observed for the following hour and discharged without symptoms of discomfort. The patients' NRS pain score was measured at baseline and each day of treatment.² For the purpose of this review, only baseline and day 14 were observed, assessing for improvement to a pain score ≤ 3 .

Due to lack of improvement after 8 days of treatment, only one participant from B₀ control group dropped out of the study. A total of 1 out of 49 participants (from group B₀ and B₁) were lost.²

At baseline, the control and intervention groups had the same mean pain scores at 8.0. After a treatment period of 14 days, 96% of group B₁ reported an improved pain score ≤ 3 . In contrast, 16% of group B₀ reported a pain score ≤ 3 .² By calculating the NNT to be 2 patients along with a CI of 1.03-1.58, these results are significant. It should be noted that the 16% with group B₀ is a similar rate to the known history of the natural decline of pain in HZ. This makes it difficult to prove any benefits of using IM MeB12. It can be concluded that the combination SC injection with MeB12 provides a significant reduction in HZ neuropathic pain, in contrast to the use of IM MeB12 with SC Lidocaine that showed little benefit to the patients.

Table 3: Pain NRS score at baseline and endpoint of intervention and control group, Xu²

Xu ²	Mean pain NRS at Baseline	% of Pts with pain NRS ≤ 3 at 14-Day Endpoint	RBI	ABI	NNT
B ₁ Intervention: SC Combo B ₁₂ + Lido	8.0 (SD 1.0)	0.96	5.00	0.8	2 patients (CI 1.03-1.58)
B ₀ Control: IM B ₁₂ + SC Lido	8.0 (SD 1.2)	0.16			

In the study conducted by Xu et al,³ 204 participants were assessed for eligibility.

Inclusion criteria were as follows: AHN from the 5th – 10th intercostal nerve ≤ 7 days after rash onset; >25 lesions on rash; aged > 50 years; severe pain on the unilateral T5-10 dermatome associated with the HZ rash and a worst pain score of ≥ 6 in the past 24 hours; and willingness to comply with the allocated treatment and follow-up measurements.³ Exclusion criteria were as follows: pain > 7 days after rash onset; neuropathic or significant pain outside the target regions; use of steroid, analgesics, or capsaicin within 4 weeks of study entry; any clinically significant medical condition or laboratory abnormality; and cognitive impairment.³

After meeting criteria, 180 participants enrolled in the study and were randomized by computer generation and distributed into control and intervention groups. Those were separated out into 4 total groups based on rash onset, a control and intervention group with onset ≤ 3 days and a control and intervention group with onset between 4-7 days. For the purpose of this review,

only the latter two groups were observed, ES-Ctl ($n = 44$) and ES-Tr ($n = 45$). The ES-Ctl group received IM MeB12 and SC lidocaine injections, while the ES-Tr group received a combination SC injection of MeB12 and lidocaine, into the subcutaneous regions of the crusted lesions where the patients experienced pain. Frequency of dosing was once daily, 6 times per week for 2 weeks. The patients were observed for the following hour and discharged without symptoms of discomfort. The patients' NRS pain score was measured at baseline and each day of treatment.³ For the purpose of this review, only baseline and day 14 were observed, assessing for improvement to a pain score ≤ 3 .

Due to lack of improvement after receiving treatment for 8 days, one patient in the ES-Ctl group did not complete the study. One other participant of this group was lost to follow up after receiving 10 days of treatment. In the ES-Tr group, one subject dropped out because of a leg fracture. A total of 3 out of 89 participants (2 of group ES-Ctl and 1 of group ES-Tr) dropped out of this study.³

At baseline, the control and intervention groups had similar mean pain scores. Group ES-Tr had a mean pain score of 8.4, while group ES-Ctl had a mean pain score of 8.3. After a treatment period of 14 days, 96% of group ES-Tr reported an improved pain score ≤ 3 . In contrast, 13% of group ES-Ctl reported a pain score ≤ 3 .³ By calculating the NNT to be 2 patients along with a CI of 1.06-1.43, these results are significant. It can be concluded that the combination SC injection with MeB12 provides a significant reduction in HZ neuropathic pain, in contrast to the use of IM MeB12 with SC Lidocaine that showed little benefit to the patients.

Table 4: Pain NRS score at baseline and endpoint of intervention and control group, Xu³

Xu ³	Mean pain NRS at Baseline	% of Pts with pain NRS ≤ 3 at 14-Day Endpoint	RBI	ABI	NNT
ES-Tr Intervention: SC Combo B ₁₂ + Lido	8.4 (SD 1.5)	0.96	6.38	0.83	2 patients (CI

ES-Ctl Control: IM B ₁₂ + SC Lido	8.3 (SD 1.2)	0.13			1.06-1.43)
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Safety and Tolerability

The injections were well tolerated overall across all studies. There were no serious injuries or adverse events noted during the interventions or during the follow up periods.^{1,2,3}

DISCUSSION

The results from all studies suggest that treatment for HZ neuropathic pain could be improved by using SC MeB12 injections. Xu¹ showed significant improvement with SC MeB12 as opposed to SC Lidocaine. Similarly, Xu² and Xu³ showed significant improvement with SC combination of MeB12 and Lidocaine as opposed to IM MeB12 and SC Lidocaine.

Due to the increase in pain severity that is correlated with the increased age of patients, it is understandable for Xu² and Xu³ to use only participants older than 50 years of age. With Xu¹ observing patients as young as 25 years old, incorporation of this study’s results into this review could provide a stronger idea of the effect MeB12 has on all ages.

If the treatment regimens used in these three studies were to be implemented in routine HZ treatment, patients would be required to receive injections 6 days per week for several weeks. This could pose an obstacle if patients have difficulty acquiring insurance. A more affordable solution could be to administer treatment during nurse visits. Depending on medication regulations, the patients can also be taught how to administer the injections at home to save them time and money on daily visits to the office.

Methylcobalamin is a common supplement, vitamin B₁₂, taken over the counter. Although the recommended daily dose for adults is 2.4 micrograms, the body will only use what it needs, allowing the kidneys to excrete any excess. In the rare cases of patients with vitamin B₁₂ deficiencies, high doses of the supplement can cause dizziness, headaches, anxiety, nausea, or

vomiting. The most common cause of deficiency is from vegetarian diets. Possible interactions with other medications causes decreased absorption of the supplement.⁹

Limitations

Limitations to the studies used involve the participants. Although the amounts of patients that dropped out were small, they still had a significant effect in combination with the small sample size of participants. A larger number of patients would need to be used in future studies to make up for the dropout rates as well as to confirm the findings of these three studies. The authors believed that a limitation in their studies was in the treatment administration. The difficulty in blinding the local treatment injections could have had a negative effect on the results.^{1,2} Additional treatment limitations involve the dosing of the medications. Xu et al¹ states that the dosing recommendations were based off of limited data. More studies need to be conducted to find the optimal dosing for treating PHN. Restrictions were also found in quantifying the pain by participants. The NRS pain scale can be subjective and difficult to regulate. Xu² states that there was concern with patients reporting their pain scores over the phone. The authors believed that pain perception may be different or even more accurate during routine monitoring visits.

CONCLUSION

The evidence presented in this review is conclusive that including SC injections of MeB12 in the treatment regimen of HZ related neuropathic pain is clinically more effective than SC lidocaine injections alone. In future studies, it would be beneficial to extend the follow up period to ensure the efficacy of treating with SC MeB12 and confirm the lack of side effects. In order to improve pain scores even further, it may be advantageous to experiment with nerve block techniques with lidocaine and MeB12, rather than only subcutaneous injections, to involve

the full nerve track affected. Clinical use of MeB12 therapy has already shown to improve symptoms of peripheral neuropathy and autonomic dysfunction.¹ The results of this review have now supported that local injections of MeB12 allows direct contact with the virus-damaged tissue to provide a neurological improvement. With continued studies to support these results, HZ patients in the future will benefit immensely.

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