Methylcobalamin as an Adjuvant Medication in Conservative Treatment of Lumbar Spinal Stenosis

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Abstract

To find out the clinical effects of methylcobalamin on the conservative treatment of degenerative lumbar spinal stenosis, the study was carried out as a control single blind trial with 2 year follow-up in 152 patients, 68 males and 84 females, whose ages ranged from 55 to 85 years, average 67 $\pm$ 18.1 years. They were randomly allocated into 2 groups, the control group, 82 patients, and the methylcobalamin group, 70 patients. All had classical history, and physical and radiographic findings which confirmed the diagnosis of spinal stenosis. Conventional management, including patient education, physical therapy and medication, were carried out in every patient and in addition methylcobalamin 0.5 mg was given orally three times a day in the methylcobalamin group for 6 months. All patients were followed up periodically for 2 years. Most of the patients in both groups showed improvement but there was no significant difference between the 2 groups in terms of pain improvement and neurological signs, except neurogenic claudication distance which was better in the M-group.

Key word : Spinal Stenosis, Vitamin B12

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J Med Assoc Thai 2000; 83: 825-831

Lumbar spinal stenosis caused by degeneration is a clinical-anatomic syndrome[1]. Patients usually present with back and lower extremity pain and discomfort, which are exacerbated by lumbar extension and relieved by flexion, and neurogenic intermittent claudication[1-3]. Patients usually have evidence of lower extremity neurological deficits[4]. The concomitant presence of degenerative changes of the lumbar spine is also the prerequisite to a development of symptomatic spinal stenosis[5].

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Conservative treatment is still the treatment of choice in patients who have degenerative lumbar spinal stenosis especially those who have mild and moderate signs and symptoms of stenosis[5-8]. Surgical treatment is strongly indicated only in the patients who have severe pain, definitive neurological deficit and sciatica[9-11].

Although the exact pathogenesis of clinical signs and symptoms is still controversial, most researchers believe that entrapment of the neural tissue in the central spinal canal, which causes disturbance of vascular circulation in the cauda equina and nerve roots and disturbance of intra-axonal circulation, is the main cause of pain and disabilities[1-4,11,12]. Some drugs such as corticosteroids, calcitonin, beraprost sodium and lipoprostaglandin E are also added in the conservative treatment programme and many studies have reported encouraging clinical effects of these substances[13-16]. All of these drugs improve circulation in the entraped neural elements in the spinal cannal[13-16]. High doses of vitamins and vitamin derivatives such as vitamin B6 have positive effects as the adjuvant therapy in nerve entrapment syndrome [17-19]. However, data from other vitamins and their derivatives are very limited. Non-steroidal antiinflammatory drugs are used in spinal stenosis and complications of the drugs are frequently observed.

We were interested in finding out the clinical effects of methylcobalmin, a methyl-vitamin B12, as an adjuvant therapy in the conservative treatment of degenerative lumbar spinal stenosis to find out the possibility of lessening the use of non-steroidal antiinflammatory drugs.

PATIENTS AND METHOD

The study was designed as a randomised controlled single blind trial with a 2 year follow-up. There were 152 patients, 68 males and 84 females, with ages ranging from 55 to 80 years. Included were clinical signs and symptoms of moderate degenerative spinal stenosis[2,3,8]. All patients had moderate to severe degenerative changes of the lumbar spine without spondylolisthesis as observed on radiographic study[5]. Exclusion criteria included the presence of digestive (including peptic ulcer), hematological, hepatic and renal disorders.

The patients were examined physically and laboratory investigations (complete blood count, urinalysis and blood chemistry for hepatic and renal functions) were also carried out to confirm the diagnosis and establish the underlying diseases. Radiography was carried out in all cases. Lumbar myelography, computed tomography scans and magnetic resonance imaging were also carried out in particular cases. If immediate surgical treatment appeared to be indicated, the patients were excluded from this trial.

Patients were all fully informed about the trial objectives, methods, and evaluation procedures, and all gave their verbal consent to participate.

Patients were randomly allocated to 2 groups according to the last 2 digits of their hospital numbers, the control (C) group and the methylcobalamin (M) group. There were 82 patients in the C-group, 37 males and 45 females, and 70 patients in the M-group, 30 male and 40 females. Demographic data and characteristics of pain and disabilities are presented in Table 1.

Conservative treatment was carried out in both groups after a definitive diagnosis was made. This included patient education, activity modification, exercises to strengthen trunk and abdominal muscles, and physical therapy. Non steroidal antiinflammatory drugs, analgesics and muscle relaxants were also given to the patients in both groups as necessary when pain and muscle tightness were moderate to severe. Vitamin B1 100 mg, B6 50 mg and B12 0.1 mg 3 times a day were also given to both groups. In the M-group, methylcobalamin, Methycobal, ESAI, 1.5 mg per day in 3 divided doses after meals, was given continuously to the patients for 6 months.

The patients of both groups were followed-up every month for 2 years. The patients were evaluated and monitored by orthopaedic surgeons who were unaware of the group to which the patients belonged. All major signs and symptoms of spinal stenosis were evaluated and compared. Adverse effects of all medications were evaluated by the patients and objectively by the surgeons. For analysis of discrete data, the Chi-square test was used and for the continuous data the Student-T-test was used.

RESULTS

Biodata of the patients in both groups were comparable (Table 1). Patients' morbidity and clinical signs and symptoms before trial in both groups were also similar (Table 1 and 2). Most of the patients in both groups showed improvement in

Table 1. Patients' characteristics and clinical signs and symptoms.

	C-group n = 82	M-group n = 70	Analysis
Gender			
Male	37	30	$x^2 = 1.3$
Female	45	40	$p > 0.05$
Age (years)			
Range	56 - 80	55 - 76	$p = 0.5$
Mean age (± SD)	66.8 ± 9.3	66.8 ± 8.4	
Occupation			
Employed	21	18	$x^2 = 2.9$
Un-employed	61	52	$p > 0.05$
Morbid period before trial (mths)			
< 1	29	25	$x^2 = 1.5$
> 1	53	45	$p > 0.05$
Pain on spinal motion			
Mild	18	15	$x^2 = 1.4$
Moderate to severe	64	55	$p > 0.05$
Lumbar range of motion			
Mild limitation (< 15 degrees)	57	49	$x^2 = 1.2$
Moderate to severe limitation (> 15 degrees)	25	21	$p > 0.05$
Straight leg raising test			
< 60 degrees	12	10	$x^2 = 2.9$
> 60 degrees	70	60	$p > 0.05$
Impairment of deep tendon reflex			
At knee			
Yes	10	6	$x^2 = 2.1$
No	72	64	$p > 0.05$
At ankle			
Yes	13	10	$x^2 = 1.7$
No	69	60	$p > 0.05$
Impaired sensation			
1 root dermatome	68	59	$x^2 = 3.3$
> 1 root dermatome	14	11	$p > 0.05$
Impaired motor function			
1 root level	76	67	$x^2 = 1.9$
> 1 root level	6	3	$p > 0.05$
Neurogenic claudication distance			
< 1000 m	59	50	$x^2 = 1.1$
> 1000 m	23	20	$p > 0.05$

all clinical signs and symptoms after treatment (Table 2). However, 2 patients in the C-group and 1 patient in the M-group had no improvement and surgical intervention was needed after 6 months follow-up and these 3 patients were excluded from the study after 12 months.

There was no significant difference between the 2 groups in terms of pain on spinal motion, limitation of spinal motion, straight leg raising test, impairment of deep tendon reflex, and impairment of sensation and motor functions (Table 2). However, patients in the M-group had significantly better improvement in neurogenic claudication than the C-group significantly (Table 2). The need for NSAID, muscle relaxants and epidural steroid injections in both groups was also similar (Table 3). There were no significant changes in blood and urine tests before and after the trial at each time of evaluation in the 2 year follow-up period. The tests included complete blood count, blood urea nitrogen, creatinine, uric acid, SGOT, SGPT, alkaline phosphatase and urine examination. No serious side-effect of any medication was observed.

Table 2. Changes of signs and symptoms during trial.

Signs and symptoms	Before trial		6 months		12 months		18 months		24 months	
	C group	M group	C group	M group	C group	M group	C group	M group	C group	M group
Pain on spinal motion										
Yes	82	70	35	30	18	14	8	8	2	-
No	-	-	47	40	62	14	72	61	78	69
Limitation of spinal motion										
Yes	82	70	64	53	56	49	54	45	54	49
No	-	-	18	17	24	20	26	24	26	24
Straight leg raising test										
< 60 degrees	12	10	4	4	-	-	-	-	-	-
> 60 degrees	70	60	78	66	80	69	80	69	80	69
Impairment of deep tendon reflex										
At knee										
Yes	10	6	-	-	-	-	-	-	-	-
No	72	64	82	70	80	69	80	69	80	69
At ankle										
Yes	13	10	2	1	-	-	-	-	-	-
No	69	60	80	69	80	69	80	69	80	69
Impaired sensation function										
Yes	82	70	13	10	7	5	-	-	-	-
No	-	-	69	60	> 3	64	80	69	80	69
Impaired motor function										
Yes	82	70	10	8	-	-	-	-	-	-
No	-	-	72	62	80	69	80	69	80	69
Neurogenic claudication distance										
< 1000 m	59	50	25	10	15	2	13	2	12	-
> 1000 m	23	20	57	62	65	67	67	67	68	69
x^2	1.19		5.1		7.7		5.9		No data	
p-value	> 0.05		< 0.05		< 0.05		< 0.05			
Surgery	-	-	-	-	2	1	(2)	(1)	(2)	(1)
Total	82	70	82	70	80	69	80	69	80	69

Table 3. The use of non steroidal antiinflammatory drugs muscle relaxant and epidural steroid during 2 year follow-up.

	C-group n = 80	M-group n = 69	P-value
Types of NSAIDS			
Tenoxican 20 mg/d	46	39	$x^2 = 2.1$
Loxoprofen 180 mg/d	34	30	$p > 0.05$
Total day of NSAID use			
< 42 days	63	54	$x^2 = 1.6$
> 42 days	17	15	$p > 0.05$
Total day of muscle relaxant (orphenadrine citrate with paracetamol) use			
< 42 days	70	60	$x^2 = 2.16$
> 42 days	10	9	$p > 0.05$
Administration of epidural steroid			
Yes	31	26	$x^2 = 1.2$
No	49	43	$p > 0.05$

DISCUSSION

Central spinal canal stenosis from degenerative changes of the spine can produce direct mechanical compression on the nerve root and cause ischemia[20-22]. The pathophysiology of this condition is a dynamic process which can be made worse in particular positions of the spine and some activities such as walking[1]. Recovery of neural deficit and pain is observed after postural correction, activity modification and medication. Non steroidal antiinflammatory drugs are commonly used in conservative treatment of this condition[23,24].

Methylcobalamin is a cofactor of methionine synthase and its function is as a methyl donor in the maintainance of DNA methylation reactions[25,26]. It also participates in the regulation of neuronal adenyl cyclase signal transduction[27,28]. In laboratory studies, it can promote regeneration of degenerating nerve terminals in the gracile axonal dystrophy mutant mouse[29] and provide neuronal protection[30]. In clinical studies, methylcobalamin showed statistical improvement in the somatic and autonomic symptoms with regression of signs of diabetic neuropathy[31] and Bell's palsy[32]. In the M-group, patients had significantly better improvement in the distance which produced neurogenic claudication than the patients in the C group (Table 2). This finding also confirmed that not only does vascular impairment play an important role in the genesis of neurologenic claudication but also that mechanical compression on the nerve is also involved in the genesis of this symptom. However, methylcobalamin has no significant effect on pain and other neurological syndromes. Even though neurogenic claudication is the most common and characteristic symptom of lumbar spinal canal stenosis, its exact pathogenesis is complex and still controversial.

SUMMARY

Methylcobalamin gave encouraging results in minimizing neurogenic claudication of degenerative lumbar spine. Further studies on the mode of action and clinical efficacy of this drug should be carried out.

(Received for publication on September 1, 1998)

REFERENCE

1. Berthelot JM, Bertrand Vasseur A, Rodet D, Maugars Y, Prost A. Lumbar spinal stenosis : a review. Rev Rheum Engl Ed 1997; 64: 315-25.
2. Nagler W, Hausen HS. Conservative management of lumbar spinal stenosis. Identifying patients likely to do well without surgery. Postgrad Med 1998; 103 : 4, 69-71, 76, 81-3.
3. Katz JN, Dalgas M, Stucki G, Lipson SJ. Diagnosis of limbar spinal stenosis. Rheum Dis Clin North Am 1994; 20: 471-83.
4. Clinchot DM, Kaplan PE, Lamb JF. Lumbar spinal stenosis in an elderly patient. J Gerontol Biol Sci Med 1998; 53: 72-5.
5. Martinelli TA, Niesel SW. Epidemiology of spinal stenosis. Instr Course Lect 1992; 41 : 179-81.
6. Herno A, Airaksinen O, Saari T, Luukkonen M. Lumbar spinal stenosis : a matchedpair study of operated and non-operated patients. Br J Neurosurg 1996; 10: 461-5.
7. Herno A. Surgical results of lumbar spinal stenosis. Ann Chir Gynaecol Suppl 1995; 250: 196-9.
8. Atlas SA, Deyo RA, Patrick DL, Convey K, Kellu RB, Singer DE. The Quebec Task Force classification for spinal disorders and the severity, treatment and outcomes of sciatica and lumbar spinal stenosis. Spine 1996; 25: 2885-92.
9. Onel D, Saritt, Donmez C. Lumbar spinal stenosis : clinical/radiological therapeutic evaluation in 145 patients. Conservative treatment or surgical treatment? Spinal 1993; 18: 291-8.
10. Niggemeyer O, Strauss JM, Schulitz KP. Comparison of surgical procedures for degenerative lumbar spinal stenosis : a meta-anlysis of the literature from 1975 to 1995. Eur Spine 1997; 6: 423-9.
11. Porter RW. Spinal stenosis and neurogenic claudication. Spine 1996; 21: 2046-52.
12. Stanby G, Evans G, Shieff C, Hamilton G. Intermittent claudlication due to spinal stenosis in a vascular surgical practice. J R Coll Surg Edinb 1994; 39: 83-5.
13. Rydenik BL, Cohen DB, Kostnik JP. Spinal epidural steroids for patients with lumbar spinal stenosis. Spine 1997; 22: 2313-7.
14. Eskolat, Pohjolainen T, Alaranta H, Soini J, Tallroth K, Sltis P. Calcitonin treatment in lumbar spinal stenosis : a randomize, placebo-controlled double-blind cross-over study with one-year

follow-up. Calcif Tissue Int 1992; 50: 401-3.
15. Kato H, Emurar S, Ngashima K, Kishikawa H, Takashima T, Ohmori K. Successful treatment of intermittent claudication due to spinal cannal stenosis using beraprost sodium, a stable prostaglandin 12 analogue. A case report. Angiology 1997; 48: 457-61.
16. Murakami M, Takahashi K, Sekikawa T, Yasuhara K, Yamagata M, Moriya H. Effects of intravenous lipoprostaglandis E 1 on neurogenic intermittent claudication. J Spinal Disord 1997; 10: 499-504.
17. Keniston RC, Nathan PA, Leklem JE, Lockwood RS. Vitamin B6, Vitamin C, and carpal tunnel syndrome. A cross-sectional study of 441 adults. J Occup Environ Med 1997; 39: 949-59.
18. Franzblav A, Rock CL, Werner RA, Albers JW, Kelly MP, Johnston EC. The relationship of vitamin B6 status to median nerve function and carpal tunnel syndrome among active industrial workers. J Occup Environ Med 1996; 38: 485-91.
19. Jacobson MD, Plancher KD, Kleinman WB. Vitamin B6 therapy for carpal syndrome. Hand Clin 1996; 12: 253-7.
20. van Akkerveekan PF. A taxonomy of lumbar stenosis with emphasis on clinical applicability. Eur Spine J 1994; 3: 130-6.
21. Verbiest H. A radicular syndrome from development narrowing of the lumbar vertebral canal. J Bone Joint Surg 1954; 36-B: 230-7.
22. Blau JN, Louge V. Intermittent claudication of the cauda equina. Lancet 1961; 1: 1081-6.
23. Deyo RA. Drug therapy for pack pain. Which drugs help which patients? Spinal 1996; 21: 2840-9.
24. Koes BW, Scholten RJ, Mens JM, Bouter LM. Efficacy of non stenoidal antiinflammatory drugs for low back pain : a systematic review of randomised clinical trials. Ann Rheum Dis 1997; 56: 214-23.
25. Pfohl-Leszkowic A, Kieth G, Dirheimer G. Effect of cobalamin derivatives in intro enzymatic DNA methylation : methycobol can act as a methyl donor. Biochemistry 1991; 30: 8045-51.
26. Rosenblatt DS, Lue-shing H, Arzoumonian A. Methyleneterohydrofolate reductase (MR) deficiency ayntheses activity and methylcobalamin levels in cultured fibroblast. Biochem Med Metab Biol 1992; 42: 221-5.
27. Yamashiki M, Nishimura A, Kosaka Y. Effects of methylcobalamin (Vitamin B12) on vitro cytokine production of peripheral blood mononuclear cells. J Clin Lab Immunol 1992; 37: 173-82.
28. Halta S, Watanabe M, Ikeda H, Kamada H, Saito T, Ohshika H. Impairment of adenylyl cyclase signal transduction in mecobalamin deficient rats. Eur J Pharmacol 1995; 291: 351-8.
29. Yamazaki K, Oda K, Endo C, Kikuchi T, Wakabayashi T. Methylcobalamin (methyl B12) promotes regeneration of motor nerve tarminals degenerating in anterior gracile muscle of gracile axonal dystrophy (GAD) metant mouse. Neurosei Lette 1994; 170-1 : 195-7.
30. Akaike A, Tamura Y, Sato Y, Yokota T. Protective effects of a vitamin B12 analog, methylcobalamin, against glutamate cytotoxicity in cultured cortical neurons. Eur J Pharmacol 1993; 241: 1-6.
31. Yoqub BA, Siddigue A, Sulimain R. Effects of methylcobalamin on diabetic neuropathy. Clin Neurol Neurosurg 1992; 94: 105-11.
32. Jalaludin MA. Methylcobalamin treatment of Bell's palsy. Methods Find Exp Clin Phormacol 1995; 17: 536-44.

ผลการใช้เมธิลโคบาลามินร่วมในการรักษาภาวะช่องสไปนัลตีบ

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รายงานผลการใช้เมธิลโคบาลามินร่วมในการรักษาภาวะ spinal stenosis โดยอนุรักษ์นิยม โดยศึกษาแบบ control single blind ติดตามผลการรักษาเป็นเวลา 2 ปี ในผู้ป่วย 152 ราย เป็นชาย 68 ราย และหญิง 84 ราย อายุเฉลี่ย 67.0 ± 18.1 ปี แบ่งผู้ป่วยเป็น 2 กลุ่ม กลุ่มควบคุม 82 รายและกลุ่มศึกษา 70 ราย ผู้ป่วยทุกรายมีประวัติและผลการตรวจยืนยันภาวะ spinal stenosis ทั้งสองกลุ่มได้รับการรักษาโดยอนุรักษ์นิยมซึ่งได้แก่ การให้ความรู้แก่ผู้ป่วย การรักษาทางเวชศาสตร์ฟื้นฟูและการให้ยา กลุ่มศึกษาได้รับยาเมธิลโคบาลามิน 0.5 มก 3 ครั้ง ต่อวัน ส่วนกลุ่มควบคุมไม่ได้รับยานี้ร่วมกับการรักษาอื่น ๆ ติดต่อกันเป็นเวลา 6 เดือน พบว่าผู้ป่วยทั้ง 2 กลุ่ม มีอาการทุเลาลงแต่ไม่มีความแตกต่างกันในด้านความปวดและความผิดปกติทางระบบประสาท ยกเว้นระยะทางที่ผู้ป่วยเดินจนมีอาการปวดจาก neurogenic claudication ซึ่งผู้ป่วยในกลุ่มศึกษาที่ได้รับเมธิลโคบาลามิน เดินได้ไกลกว่าอย่างมีนัยสำคัญ

คำสำคัญ : ไขสันหลังตีบ, วิตามินบีสิบสอง

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