นิพนธ์ต้นฉบับ

Treatment of diabetic distal symmetrical small-fiber polyneuropathy with gangliosides. (part I : clinical aspects)

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In an open-self controlled study design, therapeutic effects of gangliosides in non-insulin-dependent diabetes mellitus with distal symmetrical small-fiber polyneuropathy were evaluated. Thirty patients met the eligibility criteria, and all of them had completed the clinical trial. The control period was one month and the treatment period was two months duration. The intervention consisted of gangliosides (Cronassial$^{(R)}$) 40 mg intramuscularly once a day and 5 days a week. The outcomes consisted of subjective clinical symptoms, neurological signs, overall satisfactory rating by the patients and monitoring of side effects of gangliosides. During the investigation period, diabetic control was stabilized and monitored by HbA1. Subjective symptoms i.e. paraesthesia, neuralgical pain, burning feet showed clinically significant improvement, and the resolution on burning feet reached statistical significance ($p = 0.04$). Neurological examination related to small-fiber dysfunction also revealed some improvement, but was not statistically significant. No side effect of gangliosides was detected and the overall satisfactory rating was fair. It should be concluded that gangliosides are clinically helpful in the management of diabetic pain syndrome especially the burning feet and may be an alternative treatment of choice for this condition.

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ได้ทำการศึกษาการรักษาโรคเส้นประสาทส่วนปลายชนิด distal symmetrical small fiber polyneuropathy ในผู้ป่วยเบาหวานชนิดไม่พึ่งอินซูลินด้วยแกงกลีโอไซด์ โดยการศึกษาเป็นแบบ open-self controlled ในผู้ป่วย 30 รายที่เป็น distal symmetrical small-fiber polyneuropathy และคัดเลือกผู้ป่วยตามเกณฑ์ที่กำหนดไว้ ในการศึกษานี้มีระยะควบคุมเป็นเวลา 1 เดือน และระยะเวลาที่รักษาด้วยแกงกลีโอไซด์ (Cronassial(R)) เป็นเวลา 2 เดือน โดยการฉีดยานี้ 40 มิลลิกรัมทางกล้าม วันละครั้ง สัปดาห์ละ 5 วัน การวัดผลการศึกษาประกอบด้วยการเปลี่ยนแปลงอาการและอาการแสดงของผู้ป่วย การประเมินผลความพึงพอใจในการรักษาของผู้ป่วย การเฝ้าระวังภาวะแทรกซ้อนจากยา ในระหว่างการวิจัยได้พยายามควบคุมเบาหวานให้คงที่ และวัดผลการควบคุมเบาหวานด้วย HbA1 จากผลการวิจัยนี้พบว่า อาการในด้านความรู้สึก ได้แก่ อาการเสียวแปลบปลาบ, อาการปวด และอาการปวดแสบปวดร้อนของเท้าดีขึ้น โดยเฉพาะอาการปวดแสบปวดร้อนของเท้าดีขึ้นอย่างมีนัยสำคัญทางสถิติ (P = 0.04) อาการแสดงที่เกี่ยวข้องกับการทำงานของ small-fiber ดีขึ้น แต่ไม่พบว่ามีนัยสำคัญทางสถิติ ในการวิจัยนี้ไม่พบผลแทรกซ้อนจากแกงกลีโอไซด์ และผู้ป่วยค่อนข้างพอใจในผลการรักษา โดยสรุปผลที่เห็นเด่นชัดที่สุดของแกงกลีโอไซด์คือผลการรักษากลุ่มอาการเจ็บปวดในผู้ป่วยเบาหวาน โดยเฉพาะอาการปวดแสบปวดร้อนเท้า และยานี้อาจใช้เป็นยาที่ใช้รักษาอาการดังกล่าวได้อีกอย่างหนึ่งนอกเหนือไปจากยาอื่น ๆ ที่ใช้ในปัจจุบัน

Diabetes mellitus is a common disease that has devasating consequences for individuals, their families and the society as a whole. The prevalence of diabetes mellitus in Thailand is about 2.5%[1]. Peripheral neuropathy is the most common and most serious long term complication in diabetes mellitus. The prevalence of diabetic polyneuropathy has been estimated to range from 0-93%, depending on the method of assessment[2]. In our institution the prevalence of neuropathy in non-insulin-dependent diabetes, using medical history and physical examination, was sbout 49.6%[3].

Despite decades of intensive research, the pathogenesis of diabetic neuropathy appears unresolved and many mechanisms have been postulated. Current proposals as to causal mechanisms of diabetic neuropathy include vascular, metabolic, neurotrophic and immunological theories[4].

Therapeutic approaches to the treatment of diabetic neuropathies include glycaemic control, symptomatic treatment, especially for pain and autonomic dysfunction, and experimental treatments[5]. The rationale for experimental therapy depends on the proposed mechanism of diabetic neuropathy[5]. These therapies consist of myoinositol supplement, aldose reductase inhibitors, vitamins, vasodilators and gangliosides[5]. To date most of the treatments have not yet shown definite efficacy.

Many experimental trials have revealed that gangliosides promote nerve regeneration and accelerate reinnervation in neuropathies of various aetiologies[6]. Therefore, this mode of therapy may be useful in diabetic neuropathy.

The purpose of this study is to investigate the possible beneficial effects of gangliosides on the clinical manifestations and electrophysiological parameters in a diabetic distal symmetrical predominantly small-fiber polyneuropathy. Factors which differentiate the responders from the non-responders will be probed. This clinical trial is unique, since no previous trials focused specifically on an individual subgroup of diabetic neuropathy.

Materials and Methods

Study design: This was an open self-controlled trial. During the study period the patients were asked to stop any medication which might have an effect on neuropathy either specifically or symptomatically. A washout period of 1 month was required before the study period. During this control period of one month, the patients received regular diabetic control. In the treatment period, the patients received gangliosides 40 mg administered intramuscularly in a single dose, 5 days a week for 8 weeks. Diabetic control status was monitored by fasting plasma glucose and glycosylated haemoglobin. Good, fair and poor control are indicated by glycosylated haemoglobin of <8, 8-10 and $>10\%$ respectively.

Population : The inclusion criteria were: (1) diabetic distal symmetrical predominantly small-fiber polyneuropathy (2) age over 20 years and (3) stable diabetic control. The exclusion criteria were: (1) patients with medical or other neurological problems; (2) pregnancy (3) peripheral vascular insufficiency and (4) patients at risk of loss to follow-up. The patients were screened, interviewed and examined by a diabetologist and a neurologist at the Department of Medicine. The electrophysiological study was performed in the Department of Physical Medicine and Rehabilitation, Chulalongkorn University Hospital.

Outcome : The outcomes were improvement in signs and symptoms of neuropathy using neuropathy assessment score[7], side-effects of drugs, tolerability of medication and overall treatment rating scale from the patients. Electrophysiological response and prognostic factors will be discussed in part II and part III of this series.

Results

Population : Thirty patients fulfilled the eligibility criteria. All of them had distal symmetrical predominantly small-fiber polyneuropathy. There were 24 females and 6 males. The average age of patients was 60.4 ± 8.5 years (42-76 years). The duration of diabetes mellitus and the duration of neuropathy were 9.7 ± 6.3 years (1-20 years) and 2.1 ± 1.5 years (1-5 years) respectively. Diabetic control for 3 patients was reached with diet alone, 16 with oral hypoglycemic drugs and 11 with insulin. Status of diabetic control consisted of 21 patients with strictly stable diabetic control and 8 with mild fluctuation of control. The baseline data are summarized in Table 1. Compliance for treatment and follow-up was 100% for the study period of 3 months.

Clinical features : The cardinal features of distal, symmetrical predominantly small-fiber polyneuropathy i.e. areflexia, numbness, and decreased pinprick sensation were present in all cases. Other associated signs and symptoms of polyneuropathy were also encountered (Table 2).

Table 1. Baseline data.

Case	Age	Sex	Duration of DM (yrs)	Duration of Neuropathy (yrs)
1	76	F	20	1
2	60	F	2	1
3	58	M	10	1
4	51	F	2	1
5	64	F	10	3
6	74	M	12	1
7	62	F	8	3
8	61	F	7	4
9	57	F	10	5
10	47	M	4	4
11	70	F	10	2
12	73	F	20	2
13	69	M	20	2
14	60	F	1	1
15	57	F	4	4
16	69	F	16	5
17	71	F	14	3
18	66	F	1	1
19	62	F	8	1
20	50	F	1	1
21	60	F	17	1
22	49	F	4	1
23	42	F	6	1
24	56	F	12	2
25	51	F	10	3
26	53	F	20	1
27	56	F	10	2
28	63	M	3	1
29	66	F	20	2
30	60	M	10	3

DM = Diabetes mellitus
F = Female
M = Male
Yrs = Years

Table 2. Symptoms and signs in diabetic neuropathy.

Symptoms	*Number of patients*
Numbness	30
Neuralgic pain	10
Burning feet	15
Cramp	15
Signs	*Number of patients*
Pinprick	30
Temperature	25
Touch	27
Proprioceptive	5
Vibration	7
DTR	30
Atrophy of small muscle	5
Trophic changes	5

Changes in neuropathy assessment scores : The results of gangliosides therapy are shown in Table 3. Most of the symptoms and signs related to small-fiber neuropathy showed some improvement. However, only the symptom of burning feet reached statistical significance ($p = 0.04$). No deterioration of symptoms and signs were observed during the control or treatment period.

Overall assessment by patients : Clinical overall assessment by the patients were positive in 18 cases while 12 patients were either non-responders or minimal responders. No side effect of the drug was detected and overall satisfactory rating was fair.

Table 3. Changes in symptoms & signs after gangliosides treatment.

	Improved	No change	P-value*
Symptoms			
Numbness	8	22	NS**
Neurologic pain	8	2	NS
Burning feet	12	3	0.04
Cramp	11	4	NS
Signs			
Pinprick	12	18	NS
Temperature	9	16	NS
Touch	11	16	NS
Proprioceptive	1	4	NS
Vibration	1	6	NS
DTR	-	30	-
Atrophy	-	5	-
Trophic	-	5	-

* McNemar chi-square
** NS = No/Statistical/Significance

Discussion

Diabetic neuropathy is classified into various groups[8]. These classifications are essential for the evaluation of various interventions on diabetic neuropathy, since different forms of neuropathy may have different pathogenesis, clinical course, and response to different approaches of treatment. The most common form of diabetic neuropathy is symmetrical distal polyneuropathy[8]. This group of polyneuropathy can be further divided into various subgroups. Distal symmetrical predominantly small-fiber polyneuropathy is one of the predominantly sensory polyneuropathies in which pain and other sensation, carried by small nerve fibers, are mainly affected, while large-diameter fibers (position & vibration) are much less affected[5]. However, clinical overlapping of sensory and other abnormal neurological signs do exist[5]. From the morphometric studies, it was suggested that small-fibers usually degenerate before the large ones[9] and this represents the case of early diabetic neuropathy which will give more promising response. Our patients are clinically classified as distal symmetrical predominantly small fiber neuropathy and the average duration of polyneuropathy was 2-3 years. Thus our study population seems to be an appropriate group for demonstration of the efficacy of treatment.

Gangliosides (GAs) are included in a class of glycosphingolipids normally present at the neuronal membrane level[6]. The rationale for treatment of diabetic neuropathies with GAs is based on a number of observations. GAs play a very important role in neurotransmitter function, and GAs can stimulate nerve regeneration as well as promote neuritogenesis[10-15]. Various clinical studies[16-21] and our own preliminary reports[22-23] have revealed suggestive beneficial effects of GAs on diabetic neuropathy. GAs (Cronassial[R]) in this study were obtained from bovine brain, and consisted of GM, 21%, GD1a 40%, GD1b 16% and GT1b 19%[15].

From the previous clinical trials of GAs, the overall findings have been of a probable benefit in diabetic neuropathy. The improvement of "positive" sensory dysfunction i.e. pain, seemed to be the most prominent beneficial effect. Our results confirmed these findings especially in a subgroup of early and predominantly small-fiber polyneuropathy. Both neuralgical pain and burning feet showed clinically significant changes and improvement of burning feet reached statistical

significance. Pain in diabetic neuropathy may originate as a consequence of aberrant degenerative processes or the abnormally excitable myelinated fiber[24-25]. Gangliosides resolve the pain and this may be due to their influence on the sprouting process of the peripheral nerves, and the induction in the functional properties of membranes especially Na^+, K^+ ATPase[26]. Morphometric analyses of nerve fibre size showed a recovery to normal values following Gangliosides treatment[27].

Other modalities of signs and symptoms of diabetic neuropathy also showed some improvement especially those clinical features related to small-fiber dysfunction. However, no statistical significance was observed and this may reflect the small sample size of the study. The abnormal neurological findings, resulting from large-fiber damage, showed less impressive results and might reflect the more severe damage and longer duration of the disease process.

Conclusion

Since GAs have a low incidence of side effects and seem to have beneficial effects in diabetic pain syndrome, they may be an alternative choice for the symptomatic treatment of this syndrome.

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