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Sek Aksaranugraha

Sunee Siripompanich

Panupong Asvakiat

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See next page for additional authors

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Treatment of diabetic distal symmetrical small-fiber polyneuropathy with gangliosides. (part II : electrodiagnostic aspect)

Sek Aksaranugraha* Sunee Siripornpanich*
Panupong Asvakiat* Kammant Phanthumchinda**
Sompongse Suwanwalaikorn** Srichitra C Bunnag**

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In an open self-controlled study designed for evaluation of the therapeutic effect of gangliosides in non-insulin dependent diabetes mellitus patients with distal symmetrical small-fiber polyneuropathy, electrodiagnostic tests including motor nerve conduction velocity of median, ulnar, common peroneal and posterior tibial nerves, sensory nerve conduction velocity of median and ulnar nerves and latency study of sural nerve, F-wave conduction of median and common peroneal nerves and distal evoked potential amplitudes of all nerves tested, were performed. The pre-treatment control period was one month, the treatment period was two months (40 mg. of gangliosides IM once a day for 5 days a week). The tests were performed at the beginning and at the end of the control period and at the end of treatment period. There were statistically significant improvements in the sensory and motor nerve conduction velocities of both the median ($p=0.026$ and $p=0.008$ respectively) and the ulnar nerves ($p=0.046$ and $p=0.012$ respectively) and the sural nerve latencies ($p=0.039$) The sensory improvement in the lower extremities was related to the reduction of pain symptoms especially the burning feet. The improvement of the sensory conduction in the upper extremities might reflect subclinical response.

Reprint request : Aksaranugraha S, Department of Orthopedic and Rehabilitation Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.
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* Department of Orthopedic and Rehabilitation Medicine, Faculty of Medicine, Chulalongkorn University.
** Department of Internal Medicine, Faculty of Medicine, Chulalongkorn University.

เสก อักษรานุเคราะห์, สุนี ศิริพรพณิชย์, ภานุพงศ์ อัศวเกียรติ, กัมมันต์ พันธุมจินดา, สมพงษ์ สุวรรณวลัยกร, ศรีจิตรา บุนนาค. การรักษาโรคเส้นประสาทส่วนปลายชนิดดิสตัล ซิมเมตติคอล สมอล ไฟเบอร์ โพลีนิวโรพาที ในผู้ป่วยเบาหวานด้วยแกงกลีโอไซด์. (ตอนที่ 2 : การตรวจวินิจฉัยด้วยไฟฟ้า) จุฬาลงกรณ์เวชสาร 2534 มีนาคม ; 35 (3) 149-156

ในการศึกษาผลการรักษาผู้ป่วยเบาหวานชนิดที่ไม่ต้องการพึ่ง insulin และมีปลายประสาทชนิดเส้นเล็กเสื่อมสภาพทั้ง 2 ด้าน ด้วย gangliosides โดยการตรวจวินิจฉัยด้วยไฟฟ้าซึ่งประกอบด้วย การวัดความเร็วชักนำของประสาทสั่งการ median, ulnar, common peroneal และ posterior tibial การวัดความเร็วชักนำของประสาทรับความรู้สึก median, ulnar การวัดเวลาชักนำของประสาทรับความรู้สึก sural การวัดความเร็วชักนำ F-wave ของประสาท median และ common peroneal และการวัดความสูงของกระแสไฟที่เกิดจากการกระตุ้นประสาททุกเส้น

ระยะควบคุมก่อนการรักษาใช้เวลา 1 เดือน ระยะรักษาใช้เวลา 2 เดือน (ฉีด gangliosides 40 mg. เข้ากล้ามวันละ 1 ครั้งเป็นเวลา 5 วัน ต่อ 1 อาทิตย์) การตรวจวินิจฉัยด้วยไฟฟ้ากระทำก่อนและหลังระยะควบคุม และเมื่อสิ้นสุดระยะการรักษาอีกครั้งหนึ่ง พบว่าเมื่อเปรียบเทียบผลการตรวจก่อนและหลังการรักษาด้วย gangliosides ประสาท median ดีขึ้นอย่างมีนัยสำคัญทางสถิติ ทั้งความเร็วชักนำของประสาทรับความรู้สึก และประสาทสั่งการ ($p = 0.026$ และ $p = 0.008$ ตามลำดับ) เช่นเดียวกันประสาท ulnar ($p = 0.046$ และ $p = 0.012$ ตามลำดับ) และเวลาชักนำของประสาท Sural ($p = 0.039$) ได้ผลดีขึ้นด้วย

ผลการตรวจไฟฟ้าของประสาทรับความรู้สึกดีขึ้นที่ขานั้นมีความสัมพันธ์กับทางคลินิก ที่อาการความเจ็บลดลง โดยเฉพาะความรู้สึกร้อนเหมือนถูกไฟลวกที่เท้า ส่วนผลการตรวจไฟฟ้าของประสาทรับความรู้สึกดีขึ้นที่แขน อาจจะเกิดจาก subclinical response ได้

Electrophysiological studies provide reliable and reproducible approach to the detection and characterization of nerve, muscle, and neuromuscular junction diseases[1,2]. In the initial assessment, following the cause of neuropathy and assessing response to treatment of patients with diabetic neuropathy, electrophysiological test should always be undertaken in conjunction with clinical evaluation[1,2]. Various electrophysiological parameters were performed in our study on the treatment of diabetic neuropathy with gangliosides.

Reduction of $Na^+/K^+-ATPase$ activity may have a pathogenic role in diabetic neuropathy[3] and mixed bovine cerebral gangliosides have been shown to restore the activity of nerve $Na^+/K^+-ATPase$ in experimentally diabetic rats.[4] Studies in spontaneously diabetic mice have shown that gangliosides can restore impaired electrophysiological parameters.[5] Several controlled clinical trials have suggested that mixed gangliosides may alleviate neuropathic symptoms and/or favorably influence certain parameters of nerve function.[6-9]

Naarden reported that "there was definite improvement in nerve conductions in INSULIN-DEPENDENT diabetic patients treated with gangliosides injection, particularly noted in the median sensory conduction."[10]

The purpose of this study is to evaluate the effect of gangliosides in NON-INSULIN-DEPENDENT diabetic patients with distal symmetrical predominantly small-fiber polyneuropathy, by using electrodiagnostic investigations.

Materials and Methods

The study design, the studied population and the intervention were mentioned in the first part of this series.

The electrodiagnostic tests included the study of motor nerve conduction in the median, ulnar, common peroneal and posterior tibial nerves; sensory conduction in the median, ulnar and sural nerves, F wave conduction in the median and common peroneal nerves and distal evoked potential amplitudes of all the nerves tested. The tests were perfermed at the beginning (test I) and at the end of control period (test II), and also at the completion of gangliosides therapy (test III). The EMG machine used was the Medelec MS 92 A. Room temperature was set at 22°C. The normal values used were median sensory 62.8 ± 5.4 meters/second, median motor 54.5 ± 4.0 meters/second, ulnar sensory 56.7 ± 3.7 meters/second, ulnar motor 53.3 ± 32 meters/second, common peroneal motor 43.9 ± 4.3 meters/second and posterior tibial motor 41.8 ± 5.1[11] meters/second. Only the nerves which showed abnormality were compared. However there were no normal values for sural nerve, F were conduction and distal evoked potential amplitudes, comparision between the values of pre - and post - treatment wave performed. Criteria for the assessment of improvement in electrodiagnostic evaluations were a change of more than one standard deviation.

Six months after the completion of treatment, a follow up electrophysiological examination was conducted. conducted.

Results

Thirty patients were included in the trial. All of them had distal symmetrical small-fiber polyneuropathy. There were 24 females and 6 males. The average age was 60.4±8.5 years (42-76).

Table 1. Comaprison of percentage of NCV between second & third tests. There were 52.8% and 49.2% of median and ulnar sensory improvement and 40%, 38.2% and 55.2% of unchanged ulnar and common peronal motor conduction respectively. Only the posterior tibial nerves showed a greater deterioration (39.7%) than improvement (27.6%) or unchanged values (33.7%)

Table 1. Comparison in percentage of NCV between second and third tests.

N. test	Number	# Improved	# Unchanged	# Deteriorated
Median motor	60	30%	40%	30%
Median sensory	53	52.8%	26.4%	20.8%
Ulnar motor	60	31.7%	38.3%	30.0%
Ulnar sensory	59	49.2%	25.4%	25.4%
Common peroneal	58	20.7%	55.2%	24.1%
Posterior tibial	58	27.6%	32.7%	39.7%

Table 2. Comparison of sensory nerve conduction velocities: During the control period (period 1-2) only the ulnar nerve showed a statistically significant reduction in sensory nerve conduction velocities. However, both the median and ulnar nerves showed significant improvements ($p=0.026$ and $p=0.046$ respectively) at the end of the treatment period.

Table 3. Comparison of motor nerve conduction velocities. Only the median nerve showed a statistically significant reduction ($p=0.008$) during the control period, but both median and ulnar nerves showed significant improvement ($p=0.008$ and $p=0.012$ respectively) after the completion of the treatment period.

Table 2. Comparison of sensory nerve conduction.

N. test	N	X1 ± SD	X2 ± SD	t	p
Median					
between I & II	39	51.31 ± 5.10	50.12 ± 6.13	1.210	0.234
II & III	39	50.12 ± 6.13	52.39 ± 5.38	2.311	0.026*
Ulnar					
between I & II	32	54.05 ± 5.10	50.78 ± 6.13	2.673	0.011*
II & III	32	50.78 ± 6.13	53.09 ± 5.38	2.076	0.045*

* Statistically different at 0.05 level.

Table 3. Comparison of motor nerve conduction.

N. test	N	X1 ± SD	X2 ± SD	t	p
Median					
between I & II	39	47.69 ± 5.32	44.56 ± 4.49	3.63	0.008*
II & III	39	44.56 ± 4.49	46.86 ± 4.55	2.76	0.008*
Ulnar					
between I & II	40	47.84 ± 4.26	48.05 ± 3.47	0.365	0.716
II & III	40	48.05 ± 3.47	50.08 ± 5.41	2.620	0.012*
Common peroneal					
between I & II	33	37.96 ± 2.42	36.53 ± 2.61	1.988	0.055
II & III	33	36.53 ± 2.61	36.88 ± 4.75	0.489	0.628
Tibialis posterior					
between I & II	38	37.25 ± 4.98	36.41 ± 3.22	1.111	0.273
II & III	38	36.41 ± 3.22	36.38 ± 4.86	0.037	0.970

* Statistically different at 0.05 level.

Table 4. Comparison of sural nerve latencies. There was a definite and statistically significant improvement of sural nerve latencies at the completion of the treatment period.

Table 5. Comparison of F wave conduction. No significant changes were found in F wave conduction in all the nerves tested in both periods.

Table 6. Comparison of the percentage change in the evoked potential amplitudes between the second and third test periods.

Table 4. Comparison of sural nerve latencies.

N. test	N	X1 ± SD	X2 ± SD	t	p
between I & II	36	3.26 ± 0.57	3.22 ± 0.89	0.792	0.435
II & III	36	3.22 ± 0.89	2.86 ± 1.76	2.133	0.039*

Table 5. Comparison of Fwave conduction

N. test	N	X1 ± SD	X2 ± SD	t	p
Median					
between I & II	58	54.61 ± 8.91	53.57 ± 6.37	0.821	0.415
II & III	58	53.57 ± 6.37	53.17 ± 5.68	0.409	0.684
Common peroneal					
between I & II	58	46.56 ± 8.54	46.00 ± 7.04	0.453	0.652
II & III	58	46.00 ± 7.04	46.55 ± 8.55	0.507	0.614

* Statistically different at 0.05 level.

Table 6. Comparison in percentage of evoked potential amplitudes between the second and third tests.

N. test	Number	# Improved	# Unchanged	# Deteriorated
Median motor	60	36.7%	43.3%	20%
Median sensory	53	35.8%	30.2%	34.0%
Ulnar motor	60	18.3%	48.4%	33.3%
Ulnar sensory	59	33.9%	25.4%	40.7%
Common peroneal	58	27.6%	44.8%	27.6%
Posterior tibial	58	25.9%	34.4%	39.7%

Table 6. Only the median sensory nerves showed a greater percentage of improved values (35.8%) over "unchanged" (30.2%) and deteriorated (34.0%) values for evoked potential amplitudes. The evoked potential amplitude remained unchanged in 43.3% of the median motor nerves, 48.4% of the ulnar motor nerves and 44.8% of the common peroneal nerves tested. 40.7% of the ulnar sensory nerves and 39.7% of the posterior tibial nerves tested showed a reduction in evoked potential amplitudes.

Table 7. Comparison of changes in motor evoked potential amplitudes. There were no statistically significant changes between the first & second test periods and between the second and the third test periods for all nerves tested.

Table 8. Comparison of sensory evoked potential amplitudes. Again, no statistically significant changes were found in both median & ulnar nerves between the first and the second test periods and between the second & the thrid test periods.

Table 7. Comparison of amplitudes of motor evoked potentials.

N. test	N	X1 ± SD	X2 ± SD	t	p
Median					
between I & II	60	9.98 ± 5.53	9.99 ± 5.64	0.095	0.992
II & III	60	9.99 ± 5.64	10.63 ± 5.48	1.658	0.144
Ulnar					
between I & II	60	11.72 ± 6.10	12.30 ± 6.85	1.603	0.154
II & III	60	12.30 ± 6.85	11.54 ± 6.98	1.983	0.060
Common perneal					
between I & II	58	4.35 ± 2.42	4.03 ± 2.61	1.011	0.312
II & III	58	4.03 ± 2.61	3.99 ± 2.31	1.190	0.849
Posterior tibial					
between I & II	58	9.82 ± 5.36	10.02 ± 4.62	0.295	0.768
II & III	58	10.02 ± 4.62	10.18 ± 5.19	0.270	0.787

* Statistically different at 0.05 level.

Table 8. Comparison of Amplitudes of sensory eyoked potentials.

N. test	N	X1 ± SD	X2 ± SD	t	p
Median					
between I & II	38	14.26 ± 9.07	14.04 ± 8.37	0.288	0.775
II & III	38	14.04 ± 8.37	14.52 ± 10.09	0.564	0.576
Ulnar					
between I & II	32	15.13 ± 7.45	13.06 ± 8.20	1.359	0.183
II & III	32	13.06 ± 8.20	14.01 ± 8.74	0.592	0.558

* Statistically different at 0.05 level.

Table 9. Even though the drop out rate after 6 months follow-up period was 36% (11 out of 30), the numbers in the improved and unchanged groups for each motor NCV, sensory NCV and F wave NCV were much higher than those of the deteriorated groups (102:50, 73:41 & 57:19 respectively).

Table 9. Comparison of all tests between the end of the treatment and 6 months washout period.

	Nerves	Improved	Unchanged	Total	Deteriorated
Motor					
	Median	14	9	23	15
	Ulnar	14	10	24	14
	Common peroneal	12	16	28	10
	Posterior tibial	10	17	27	11
				102	**50**
Sensory					
	Median	17	8	25	13
	Ulnar	15	9	24	14
	Sural	6	18	24	14
				73	**41**
F wave					
	Median	16	13	29	9
	Common peroneal	14	14	28	10
				57	**19**

Discussion

Electrodiagnostic confirmation of abnormalities in clinical sensory nerve conduction velocities are shown in table 2 (39 median and 32 ulnar nerves). Although all patients have minimal clinical motor weakness, there are abnormalities in motor nerve conduction velocities shown in table 3 (39 median, 40 ulnar, 33 common peroneal and 38 posterior tibial nerves) which reflect their subclinical motor neuropathy.

On comparing pre- and post-ganglioside treatment (table 1, 2 & 3) changes in sensory nerve conduction velocities, and improvement is seen in 52.8% ($p=0.011$) in the pre-treatment control period followed by a significant improvement ($p=0.046$) at the end of the treatment period. This finding objectively confirms the effect of gangliosides in the improvement of sensory nerve function.

Table 3 shows that the initially abnormal median and ulnar motor nerve conduction velocities improve significantly ($p=0.008$ and $p=0.012$ respectively) at the end of the treatment period. The effect is greater in the case of median motor nerve conduction velocities which showed a significant reduction ($p=0.008$) during the control period. Since there is no clinical motor improvement seen in these patients, this finding might indicate subclinical improvement as well as that seen during the initial subclinical neuropathy.

Most Thai people do not wear proper shoes and socks which might cause the skin of their feet to be thicker and thus result in the rather high percentage (40%) of initially non-responsive antidromic sural nerve stimulation. The rest of them responds well and shows significant improvement at the completion of the treatment period as shown in table 4 which confirms their clinical sensory improvement in their lower extremities.

The unchanged F wave during the treatment period shows that the proximal involvement of the spinal nerve root in this group of patients are less prominent than that of distal portions.

Although pharmacological experiments have clearly demonstrated that exogenous ganglioside administration reduces the extent of axonal atrophy[12] our neurophysiological test shows no significant changes in the motor and sensory evoked potential amplitudes after the treatment. The reason for this finding might be that the demyelination would respond better to the gangliosides therapy than that of the degeneration of axons which are the physiological tests.

Clinically, the neurologist found only sensory improvement in the lower extremities of our patients especially the reduction of pain sensation. The electrodiagnostic findings confirmed their clinical sensory improvement in the lower extremities but not in the upper extremities which might reflect the subclinical response.

Even though the follow-up rate was only 64%, the available electrophysiological data indicated that the effect of gangliosides may last up to 6 months after treatment.

The improvement in the electrophysiological tests were demonstrated both in the sensory and motor nerves while the clinical improvements were detected mainly in the sensory symptoms. We may conclude that the electrodiagnostic tests are a more sensitive tool for the detection of improvement than the clinical assessments.

Conclusion

Using electrodiagnostic evaluations, gangliosides therapy proved to be helpful in the treatment of diabetic sensory neuropathy in non-insulin dependent diabetic patients with distal symmetrical predominantly small-fibre polyneuropathy. These results reflect those obtained by Naarden[10] in insulin-dependent diabetic patients. Due to the beneficial effects of gangliosides and their low side effect profile, they may be considered as an alternative in the treatment of diabetic pain syndrome.

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