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GM_1 GANGLIOSIDES IN THE TREATMENT OF SPINAL CORD INJURY: REPORT OF PRELIMINARY DATA ANALYSIS

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Abstract. A prospective, randomized, placebo-controlled, double-blinded spinal cord injury GM_1 ganglioside drug trial was completed. Of the 37 patients entered over a 16 month period, 34 patients (23 cervical and 11 thoracic injuries) received the test drug protocol and completed the one year follow up period. The neurologic recovery was quantified by serial measurement of the ASIA motor score throughout the acute hospital course and one year long follow up period. The primary variable used to assess neurologic recovery was the difference in the ASIA motor score from the admission value to the value at one year. The GM_1 group had an average motor recovery of 36.9 points whereas the placebo group had an average change of 21.6 points (t-test difference, $p = 0.088$). Analysis of the secondary variable, the area under the ASIA motor score versus the logarithm of time, and the use of rank order nonparametric statistic on both the primary and secondary variables to sort neurologic recovery obtained similar statistical differences between the GM_1 and placebo treatment groups. Randomization imbalances in base-

line severity of injury and division of cervical and thoracic injury occured in the trial. Because of this fact and the small sample size of the study verification of these results by a larger study is required.

INTRODUCTION

Gangliosides are complex glycolipids of an acid nature that are present in high concentrations in central nervous system cells. They are a major component of the cell membrane and occur in the highest concentration at the synaptic junction. An exciting property of gangliosides is their stimulation of the growth of nerve cells and of the regeneration of damaged nervous tissues in many experimental animal models. These encouraging experimental results led to clinical trials in diabetic neuropathy and stroke which suggested a positive effect of the gangliosides on neurologic recovery (refs. 2-16). The present study examines the recovery of motor function after spinal cord injury in humans. The spinal cord injury model was chosen to examine neurologic recovery because the motor examination can be accurately quantified and it is well known from historical data that many spinal cord injury patients go through a recovery of motor function that encompasses several months. The study was designed to test whether or not the recovery of motor function could be altered with the addition of gangliosides to the medical and surgical therapy that patients initially receive.

METHODS

A prospective, randomized, placebo-controlled, double-blinded spinal cord injury GM_1 Ganglioside drug trial was completed. Of the 37 patients entered over a 16 month period, 34 patients (23 cervical and 11 thoracic injuries) received the test drug protocol and completed the one year follow up period.

These patients were 18 years of age or older and had a spinal cord injury with a major neurologic deficit but no other significant injuries or preexisting illness. The first dose of study drug was administered within 72 h of the injury and then 18 to 32 additional 5 ml daily injections of 100 mg GM_1 or placebo were given.

The neurologic recovery was quantified by serial measurement of the ASIA motor score throughout the acute hospital course and one year long follow up period. The ASIA motor scale (ref. 1) has a range of 0 (complete quadriplegia) to 100 (normal motor function). Five key muscles in each extremity are assessed on a 0 to 5 point strength scale. Multiple neurologic determinations of motor and sensory function were

made throughout the acute hospital course and one year long follow up period.

The primary variable used to assess neurologic recovery was the difference in the ASIA motor score from the admission value to the value at one year. The secondary variable was the area under the ASIA motor score versus the logarithm of time curve.

All patients admitted to The Shock Trauma Center with a spinal cord injury were considered for entry to this study. The criteria for entry were: (1) consent obtained; (2) no contraindication to the use of GM_1; (3) female patients either had to be surgically sterile or postmenopausal; (4) age 18 years or older; and (5) spinal cord lesion with a major motor deficit of 3/5 in the hands or legs. The criteria for exclusion were: (1) premorbid major medical illness (i.e. end-stage diabetes, heart disease, etc.); (2) high likelihood of being lost to follow up; (3) involvement in other experimental drug protocols; and (4) presence of significant cauda equina damage.

RESULTS

The GM_1 group had an average motor recovery of 36.9 points from their initial score to the score at one year follow up, whereas the placebo group had an average change of 21.5 points (t-test difference, $p = 0.088$). The initial and final scores, the difference between the two, and their standard deviations are listed in Table I for the complete study group of cervical and thoracic injuries and Table II for cervical injuries only.

TABLE I

Cervical and thoracic spinal cord injury patients — mean and standard deviation of ASIA motor scores

	GM_1 treatment Group ($n = 16$)	Placebo Group ($n = 18$)
Initial motor score	25.9±21.8	39.9±20.8
Final motor score	62.8±26.8	61.4±26.5
Difference in motor score	36.9±28.2	21.5±22.9

TABLE II

Cervical spinal cord only injury patients — mean and standard deviation of ASIA motor scores

	GM_1 treatment Group ($n = 12$)	Placebo Group ($n = 11$)
Initial motor score	17.5±18.3	33.1±24.5
Final motor score	60.4±28.5	64.8±31.7
Difference in motor score	42.9±28.4	31.7±21.7

Although a trend toward a positive drug effect is present in the patients with cervical injury only, the difference in motor recovery between the GM_1 and placebo treatment group is not statistically significant (t-test difference, $p = 0.313$).

The ASIA motor score versus time curve disclosed: (1) a delay in the recovery of spinal cord injury with 50% of the ultimate one year motor recovery occurring at a geometric mean of 80 days. (2) Division of the patients' total motor point gain from admission to one year follow up into four regions each with a similar number of patients: no recovery, low recovery (3 to 14 point change in ASIA score), medium recovery (15 to 43 point change), and high recovery (44 to 99 point change). The total number in each of these groups was 7, 9, 10 and 8, respectively. The division between the GM_1 treatment and the placebo group is listed in Table III. Table IV lists the distribution of the cervical spinal cord

TABLE III

Total group ($n = 34$) of cervical and thoracic spinal cord injury patients. Number and row percentage for treatment groups in each recovery category

	No recovery	Low recovery	Medium recovery	High recovery
GM_1 treatment group	1 (6.3%)	4 (25.0%)	6 (37.5%)	5 (31.3%)
Placebo treatment group	6 (33.3%)	5 (27.8%)	4 (22.2%)	3 (16.7%)
Total number of patients in each recovery group	7 (20.6%)	9 (26.5%)	10 (29.4%)	8 (23.5%)

TABLE IV

Subgroup ($n = 23$) of cervical spinal cord only injury patients. Number and row percentage for treatment groups in each recovery category

	No recovery	Low recovery	Medium recovery	High recovery
GM_1 treatment group	0	3 (25.0%)	4 (33.3%)	5 (41.7%)
Placebo treatment group	0	5 (45.5%)	3 (27.3%)	3 (27.3%)
Total number of patients in each recovery group	0	8 (34.8%)	7 (30.4%)	8 (34.8%)

injured patients only. The no recovery patients were all thoracic injury patients. Note the randomization imbalance generated by the double-blinded nature of the study design which assigned more thoracic injuries to the placebo group.

When the number of patients receiving GM_1 or placebo in the no and low recovery groups is compared with those in the medium and high recovery groups for the complete study group of cervical and thoracic injuries, the Fisher Exact Test, Two-Tail, detected a beneficial effect of GM_1 on motor improvement ($p = 0.100$). However, when the Fisher Exact Test, Two-Tail, analyzed the cervical only injuries, a suggestive but not statistically significant improvement was noted ($p = = 0.400$).

Analysis of the secondary variable, the area under the ASIA motor score versus the logarithm of time, and the use of rank order nonparametric statistics on both the primary and secondary variables to classify neurologic recovery obtained similar statistically significant differences between the GM_1 and placebo treatment groups for the complete study group. However, these analyses revealed only suggestive trends without statistical significance in the cervical only subgroup. These tests along with the p values are summarized in Table V.

TABLE V

Comparison of statistical analysis

Data tested	Statistical test	Total group ($n = 34$)	Cervical only ($n = 23$)
Total motor change	Student's t-Test	$p = 0.088$	$p = 0.313$
Total motor change	Fisher Exact Test (Two-Tail)	$p = 0.100$	$p = 0.400$
Area under log recovery curve	Fisher Exact Test (Two-Tail)	$p = 0.045$	$p = 0.193$
Total motor change	Mann-Whitney U test for rank order	$p = 0.105$	$p = 0.448$
Area under log recovery curve	Mann-Whitney U test for rank order	$p = 0.101$	$p = 0.393$

DISCUSSION

These results demonstrate an improvement in the recovery of motor function after spinal cord injury with GM_1 ganglioside compared to placebo. However, the small sample size of this study along with ran-

domization imbalances in baseline severity of injury and type of injury require verification of these results by a larger study and further statistical analysis.

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