Effect of Prostaglandin E1 on entrapment neuropathy of diabetic rats
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INTRODUCTION:
The diabetes mellitus (DM) is often associated with entrapment neuropathy, such as carpal tunnel syndrome (CTS). In CTS, repetitive trauma and ischemia are thought to be important in its pathogenesis [1]. We hypothesized that optimization of blood flow may be beneficial for entrapment neuropathies associated with DM. It is well known that DM rats housed in a grid cage develop a hindfoot tibial mononeuropathy (tarsal tunnel syndrome) [2]. We speculate that TTS rat model has two independent factors, i.e. repetitive trauma and impaired circulation, that increase the vulnerability of nerve. Prostaglandin E1 (PGE1) has various vasotropic effect. The purpose of the present study was to investigate the effect of PGE1 on entrapment neuropathy of the diabetic rats.

MATERIALS AND METHODS:
Animal models
Twenty nine male Sprague-Dawley rats of seven weeks old were used for the experiment. Twenty three rats were made diabetic by a single intraperitoneal injection of streptozocin dissolved in citrate buffer. Nondiabetic rats were injected the citrate buffered solution as normal group. Hyperglycemia was verified 1 week after injection by sampling from a tail vein. The fasting blood glucose level of 300mg/dl or over was our criterion for experimental diabetes. DM rats were divided into three groups: 1) control (untreated) group; 2) 30 μg/kg treated group; 3) 100 μg/kg treated group. In treated rats, PGE1 was given via gastric tubing at a daily for 4 weeks. Diabetic (treated and untreated) rats were raised on wire grid flooring, non diabetic rats were raised on sawdust covered plastic flooring.

Electrophysiological examination
At zero, two and four weeks after starting the administration, electrophysiological recordings were made. Motor conduction velocity (MCV) and amplitude were recorded to estimate electrophysiological function.

Behavioral testing
1. von Frey hair (VFH) test
Paw withdrawal threshold in response to a mechanical stimulus was determined using a series of filaments of varying thickness. At zero, two and four weeks after starting the administration, test was performed.

2. Gait analysis
At four weeks after starting the administration, detailed analysis of gait was performed on walking rats using the Cat Walk (Noldus, Wageningen, Netherlands) methods. Parameters were analyzed (max contact max mean intensity, tibial functional index (TFI)).

Histological examinations
At the end of the experiment (four weeks after starting administration), both tibial nerves were quickly removed by incision. Transverse semithin section of the tibial nerves were stained with toluidine blue and used for morphometric analysis of myelinated fiber size, fiber density.

RESULTS:
Electrophysiological examination: Motor conduction velocity at baseline was not significantly different among four groups. In the normal group at two and four weeks, the MCV was significantly faster than the other groups (p<0.001). In the treated group (30 μg and 100 μg) at four weeks, the MCV was significantly faster than the control group (p<0.05). Amplitude at baseline and two weeks was not significantly different among four groups. But in the normal group at four weeks, the amplitude was significantly greater than the other groups (p<0.001). In the treated group at four weeks, the amplitude was significantly greater than the control group (p<0.05).

DISCUSSION:
The present study shows that PGE1 can partially prevent deterioration of electrophysiological and behavioral function in the DM entrapment neuropathy model. Better protection at lower dosage excludes the possibility of dose dependency but suggests the presence of optimal concentration. Some explanations might be possible for mechanism of the effect. Besides increased oxygen delivery through its vasotropic effects, PGE1 might have direct effects on neurons. For example, PGE1 was found to inhibit synaptic transmission in adrenergic and cholinergic nerve terminals [3]. More study is needed to reveal the pharmacological mechanism, we believe that PGE1 can be a potential first line drug for CTS patients associated with DM.

Significance: This study appear to expand the window of opportunity of conservative treatment for CTS patients with DM who generally show poor response to local steroid injection.

REFERENCES:

Fig1. Motor conductive velocity
Fig2. Amplitude
von Frey hair test: The mechanical withdrawal threshold at baseline and two weeks was not significantly different among four groups. In the normal group at four weeks, the withdrawal threshold was significantly higher than the other groups (p<0.001). In the treated group at four weeks, the withdrawal threshold was significantly higher than the control group (p<0.05).

Fig3. von Frey hair test
Gait analysis: In the control group at four weeks after starting of the administration, intensity was significantly lower than the normal group (p<0.01). In the treated group, intensity was significantly higher than the control group (p<0.05).

Fig4. Max contact max mean intensity
Fig5. Tibial functional index
Histological examinations: Fiber density was not significantly different among four groups. But in the control group and 30 μg group, fiber density tend to be lower than the normal group. In the 100 μg group, fiber density tend to higher than the control group. Fiber size was not significantly different among four groups.

Fig6. Fiber density
Fig7. Fiber size

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