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Effects of Hypertonic Dextrose Injections in the Rabbit Carpal Tunnel

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Abstract

Objective—This study investigated the effects of different doses of hypertonic dextrose injection on the carpal tunnel subsynovial connective tissue (SSCT) and median nerve in a rabbit model.

Methods—Thirty-eight New Zealand white rabbits weighing 4.0–4.5 kg were used. One forepaw carpal tunnel was randomly injected with one of five different treatments: saline-single injection; saline-two injections one week apart; 10% dextrose-single injection; 20% dextrose-single injection; or 10% dextrose- two injections one week apart. Animals were sacrificed at 12 weeks after the initial injection and were evaluated by electrophysiology (EP), SSCT mechanical testing and histology.

Results—There were significant increases in the energy absorption of the SSCT in the 10% dextrose double injection group compared to the saline injection groups. SSCT stiffness was also significantly increased in the 10% dextrose-double injection group compared to the other groups. There was a significant increase in the thickness of the SSCT in the 10% dextrose-double injection group compared to the saline-single injection group and a significant decrease in the nerve short-long diameter ratio in the 10% dextrose double injection group compared to the saline-single injection group. There were no changes in EP among the groups.

Conclusions—SSCT fibrosis is present for up to 12 weeks after dextrose injection; multiple injections have bigger effects, including what appears to be a secondary change in nerve flattening. This model may be useful to study the effects of external fibrosis on nerve morphology and physiology, such as occurs clinically in carpal tunnel syndrome.

Keywords

Carpal Tunnel Syndrome; Animal Model; Subsynovial Connective Tissue; Dextrose Injection

INTRODUCTION

Carpal tunnel syndrome (CTS) is a chronic compression neuropathy of the median nerve at the wrist. It is extremely common, with a prevalence that has been reported to be as high as 3%^{1,2} and an incidence that increases with age.³ Despite its everyday occurrence, however, most cases of CTS are idiopathic.⁴ Idiopathic CTS is associated with non-inflammatory fibrosis and thickening of the subsynovial connective tissue (SSCT) within the carpal tunnel.⁵ Some clinicians have hypothesized that this fibrosis might be the cause of the nerve compression.^{6,7} Yet, while several studies have investigated the pathophysiology of acute

external compression of the median nerve,^{8,9} there have been few attempts to study the chronic nature of this disease in vivo. Two previous studies have demonstrated that a single injection of 10% dextrose can induce SSCT fibrosis in a rabbit model, with some suggestion of an effect on nerve function.^{10,11} Given this interesting preliminary finding, we wished to determine if there might be a dose-response effect and whether a larger single dose might result in a different response than two smaller doses totaling the same amount of dextrose. The purpose of this study was, therefore, to investigate the effects of different doses of hypertonic dextrose on rabbit carpal tunnel tissues and on median nerve morphology and to compare these results with those previously reported.¹⁰

METHODS

Surgical Procedure

The experimental protocol was reviewed and approved by our Institutional Animal Care and Use Committee and complied with the guidelines for laboratory animals. Thirty-eight New Zealand white rabbits weighing 4.0–4.5 kg were used. Following the induction of anesthesia, electrophysiological testing (EP) of the median nerve in each fore paw was performed as described below. Then the rabbit carpal tunnel was identified by locating a small but easily palpable nodule of subcutaneous cartilage which, in the rabbit, forms part of the transverse carpal ligament. Using this landmark to locate the carpal tunnel, a 3.0–4.0 mm incision was made in the paw 1 cm proximal to the carpal tunnel. The flexor tendons were identified and the middle digit flexor digitorum superficialis (FDS) tendon was identified by moving that digit passively. A 30 gauge needle was inserted along the surface of the middle digit FDS to ensure that the injection was made into the synovium between the middle digit FDS tendon and the transverse carpal ligament. The distal extent of needle penetration was confirmed by placing the same size needle on the skin surface. One fore paw of each animal was randomly assigned to one of two variations of a similar dose of dextrose, a single injection 0.1 ml of 20% dextrose (n=18); and two injections, one week apart, of 0.1 ml of 10% dextrose (n=20). Each contralateral paw was injected with 0.1 ml of 0.9% saline to serve as a control. Twelve weeks after the initial injection, the rabbits were anesthetized for the EP test (n=12 for each group) and then sacrificed. The paws were then harvested for SSCT mechanical evaluation (n=12 for each group). The animals not used for mechanical evaluation were evaluated for either nerve or SSCT histology. The data of a single injection of 10% dextrose was referred from a pilot study.¹⁰

Evaluation of Subsynovial Connective Tissue

Mechanical Testing

After sacrificing the animals, the fore paws were harvested with the carpal tunnel intact. The method has been described previously.¹² In brief, the FDS tendons were exposed at the antebrachial level, the middle digit FDS tendon was divided at a level 5 mm proximal to the proximal edge of the flexor retinaculum and the proximal end of the middle digit FDS tendon was sutured with 5-0 Vicryl as an anchor cable. The specimen was then mounted in a custom fixture. The fixture was mounted on a custom-made microtester, which was composed of a linear servo motor (MX 80 Daedal, Irwin, PA, USA) and a load cell with the accuracy of 0.01N (MDB-5, Transducer Techniques, Temecula, CA, USA). The anchor cable was connected to the load cell. The middle digit FDS tendon was then sharply cut 5 mm distal to the distal edge of the carpal tunnel.

Under displacement control, the middle digit FDS tendon was moved through the carpal tunnel at a rate of 0.5 mm/s. The load cell measurements and displacement were recorded through a LabVIEW program (National Instruments, Austin, TX, USA). Throughout testing, the specimen was kept moist by spraying saline solution. The ultimate tensile load, the

energy absorption and the stiffness of the SSCT surrounding the middle digit FDS tendons were analyzed.¹⁰ The ultimate tensile load and energy absorption were defined as the maximum load and the area under the load/displacement curve, respectively. The stiffness was defined as the slope of the load/displacement curve. For the stiffness measurement, the displacement at the ultimate tensile load was defined as 100% (the ultimate load displacement). The stiffness was then measured for each 10% increment of displacement until the ultimate load displacement.

Histological Analysis

After primary fixation in 4% paraformaldehyde solution for 24 hours, the tissue selected for SSCT histology (n=6–8) was immersed in formalin and embedded in paraffin for the secondary fixation. Five micron cross sections were made through the carpal tunnel and stained with standard hematoxylin and eosin (HE). Specimens were evaluated under light microscopy (BLX51, Olympus Co., Tokyo, Japan) for cellularity, neovascularization, fibrosis and inflammation. In addition, the shortest distance between middle finger FDS tendon and flexor digitorum profundus (FDP) tendon, and the average of the shortest distance between index and middle, middle and ring finger FDS tendons were measured at the mid-carpal tunnel level with image J software (National Institute of Mental Health, MD, USA) (Figure 1-a).

Evaluations of Median Nerve

Electrophysiological Analysis

Electrophysiological testing (EP) was performed on the median nerve of each forepaw under general anesthesia, administered as described above. The compound muscle action potential (CMAP) was recorded from the thenar muscle with stimulation of the median nerve 3.0cm proximal to the recording point. Stimulation was carried out until a supramaximal response was visualized on the monitor. Recording was performed before injection and 12 weeks after initial injection, immediately prior to sacrifice. The distal motor latency and amplitude of CMAP were measured. The evaluation was made by the ratio, which was defined as the 12 weeks value divided by the initial value as a percentage, for both latency and amplitude.

Histological Analysis

After primary fixation in 4% paraformaldehyde solution for 24 hours, the tissue selected for nerve histology (n=6–8) was immersed in a fixative solution of 10% glutaraldehyde and 10% paraformaldehyde for the secondary fixation. The tissue was embedded in plastic resin. 0.6 μ m cross sections of the median nerve were made at the carpal tunnel level and stained with toluidine blue. Sections were evaluated qualitatively under light microscopy (BLX51, Olympus Co., Tokyo, Japan) for fascicular demyelination and subperineurial edema.

In addition, the short and long cross sectional diameter ratio of the median nerve was measured from the HE stained slides with image J software (National Institute of Mental Health, MD, USA) (Figure 1-b). To measure the short-long diameter ratio, the long diameter (axis) was defined as the longest diameter of the median nerve, while the short diameter was defined as the longest diameter which was perpendicular to the long axis. The short diameter was divided by the long diameter to generate the ratio.

Statistical Analysis

One-factor Analysis of variance (ANOVA) followed by the Scheffe's post hoc test was chosen for analyzing variables. The results were expressed as mean $\pm$ standard deviation. Significant differences were defined by $P < 0.05$. In addition, Spearman's correlation test was performed to estimate the correlation between the SSCT thickness and the nerve short-long

diameter ratio. All statistical analyses were performed with the statistical package Statcel QC for Excel (OMS-publishing. Inc., Japan).

RESULTS

Evaluations of Subsynovial Connective Tissue

The ultimate load was greater in the dextrose injection groups, but the difference did not reach statistical significance (Figure 2-a, $P=0.08$). There were significant increases in energy absorption (Figure 2-b, $P<0.05$) and stiffness (Figure 3, $P<0.05$) in the 10% dextrose-double injection group compared to the saline injection controls.

The SSCT was irregular and thickened in the dextrose groups (Figure 4). The thickness of the SSCT was significantly larger in the 10% dextrose-double injection group compared to the previously reported¹⁰ saline-single injection group (Figure 5, $P<0.05$).

Evaluations of the Median Nerve

The nerve short-long diameter ratio was significantly lower in the dextrose injection groups than in the saline-single injection group (Figure 6). Evaluating all the histology specimens together, there was a significant correlation between FDP-FDS thickness and nerve short-long diameter ratio ($r=0.39$, $p<0.05$). There was no evidence of nerve demyelination histologically.

There were no significant differences in the EP test for any group or comparison. The ratios of the latency were 0.97 (0.15), 0.97 (0.09), 1.11 (0.22), 0.99 (0.13), 0.97 (0.08) in the saline-single, saline-double, 10% dextrose-single, 20% dextrose-single and 10% dextrose-double injections, respectively. The ratios of the amplitude were 1.05 (0.46), 1.16 (0.60), 0.78 (0.27), 1.28 (0.62) and 1.05 (0.56) in the saline-single, saline-double, 10% dextrose-single, 20% dextrose-single and 10% dextrose-double injections, respectively.

DISCUSSION

The mechanism by which hypertonic dextrose injection induces fibrosis is well explored elsewhere^{13–20}. Indeed, this induction of fibrosis is the basis for the use of hypertonic dextrose therapeutically, in the form of prolotherapy^{21–28}. Our concern is not how hypertonic dextrose induces fibrosis, but whether fibrosis in the SSCT can induce a median neuropathy, i.e., CTS. Our overall goal is to create a model in which we can study CTS etiology. In that regard, previously we have shown that our model has a similar SSCT structure to the human case, and that our intervention, dextrose injection, produces a histological appearance of the SSCT similar to that seen in CTS, along with early changes in nerve physiology similar to those seen in CTS. While this evidence is suggestive of a cause and effect relationship between SSCT fibrosis and the development of CTS, it is not definitive proof. We wished therefore to obtain additional evidence, specifically to see if there were a dose-response relationship, such that increasing dextrose dose resulted in more severe nerve changes. This manuscript provides evidence that increasing fibrosis results in significant flattening of the median nerve, which we believe further strengthens the relevance of this model to the study of CTS, although we acknowledge that this measurement is somewhat subjective and that the electrophysiology data did not show a corresponding change at the single, medium term time point studied.

Specifically, in this study, we have extended the results of previous studies^{10,11} that have shown that 10% dextrose injection causes increased stiffness of the SSCT compared to saline injections. We have now also shown that the injection increases SSCT thickness and that adding a second injection of 10% dextrose appears to increase this effect, while an

increase in dose to 20% as a single injection does not. The reason for this difference in effect between two 10% injections and a single 20% injection is not clear, but may relate to the difference in osmotic effect in these two variations.

Interestingly, we observed that the effect of 10% dextrose was more pronounced with multiple injections. This did not appear to be an effect of the injection, but rather the dextrose, as we found no difference in SSCT fibrosis when comparing the saline-single and saline-double injection groups. Clinically, prolotherapy is often provided by a series of injections^{22–24,26–28}; our data tend to validate this practice.

While the 10% and 20% dextrose demonstrated effects on the SSCT, they did not appear to have a direct effect on nerve function. There was, however, evidence of significant changes in nerve overall morphology in the form of nerve flattening. This suggests an external compression effect, similar to the external compression and median nerve flattening seen in clinical cases of carpal tunnel syndrome.²⁹ We did not note significant differences in nerve conduction or evidence of demyelination, however. This suggests that, despite the evident fibrosis and SSCT thickening, findings also seen in clinical CTS, the pressure within the rabbit carpal tunnel did not rise to sufficient levels to affect nerve function in our model. There are several possible explanations for this. First, the compliance of the carpal tunnel may be different between human and rabbits. Second, the median nerve anatomy is different between human and rabbit, with several small and separated fascicles in the rabbit median nerve, compared to a single large nerve trunk in the human nerve. The smaller and more dispersed rabbit fascicles may be less vulnerable to compression than one large nerve trunk.³⁰

Previous studies reported that 10% dextrose injected in to the SSCT was associated with changes in nerve histology¹¹ and distal motor latency.¹⁰ Although we observed some fascicles with qualitatively smaller axons, there was no consistency in this finding and so a formal statistical assessment was not done. The nature of this assessment and its effect on the statistical methods may also have had an effect on our ability to demonstrate a significant difference. The previous studies compared the effect of dextrose with controls within animals, using the paired t-test. This study involved multiple between animal comparisons and was therefore analyzed by one-way analysis of variance (ANOVA). Much larger sample sizes would be needed in our study to match the statistical power of the previous one. In the interest of minimizing animal use and with the idea that we were most interested in large changes, we kept our sample size relatively small. Larger sample sizes might have shown a significant difference in EP.

We believe that the model described here has several potential uses. As noted in previous studies,^{10,11} it can be useful as a model of CTS. We have confirmed here that there is at least some evidence of a dose effect on the SSCT, with evidence of nerve flattening and without any evidence of a direct noxious effect of the dextrose on nerve function. We also believe that this model may be useful to study the effects of various prolotherapy agents, as in a single model we can evaluate both the therapeutic effect on a model soft tissue, the SSCT and any noxious effect on an adjacent structure that an ideal prolotherapy should not harm, the median nerve.

There are several limitations in this study. First, we did not try to assess the mechanisms of the action by detecting specific collagen or cytokine expression. Now that we have shown that dextrose has a longer term effect at 12 weeks, it would be appropriate to study shorter term effects on cytokine expression in this model, using the known expressions from previous prolotherapy studies, cited above, as a guide. Earlier time points may also be relevant to investigate the possibility that the fibrosis is mediated in its initial phases by

local, transient inflammation. If this were true, it might present some novel options for early intervention in patients at risk for CTS. Second, as noted above, the multiple comparisons necessitated a change in statistical method in comparison to previous studies, which reduced the statistical power. In addition, our histological measurements were performed by a single observer. In the future we plan to obtain inter and intraobserver reliability measures for these methods. Third, we did not measure the local concentration of dextrose after the injections. An in vitro study of hyperglycemic effect suggested that an increase in pericellular glucose concentration above 35mM induces hyperglycemic stress and cell injury.³¹ Our initial dose is far larger, and while we cannot estimate what the local pericellular concentration might be, there may be some variability in results due to variations in the local concentration of dextrose in vivo. Fourth, since we only evaluated a single time point, we have no data on the time course of the changes we observed. Now that we have confirmed an effect, it will be important to look at other time points, with a larger number of animals.

In conclusion, hypertonic dextrose injections produced fibrosis in the rabbit SSCT, with evidence of flattening of the median nerve. This effect was more pronounced with multiple injections rather than a higher dextrose concentration. This suggests that there may be an optimum concentration and duration of stimulation needed to promote fibrosis. This model may be helpful to study the effect of synovial fibrosis on the development of CTS.

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Figure 1. Histological Measurements

a. Subsynovial Connective Tissue Thickness

1: FDS-FDP Thickness, 2: FDS-FDS Thickness

The shortest distance between middle finger FDS tendon and flexor digitorum profundus (FDP) tendon, and the average of the shortest distance between index and middle, middle and ring finger FDS tendons were measured at the mid-carpal tunnel level.

b. Nerve Short-Long Diameter Ratio

1: Short Diameter, 2: Long Diameter

The short and long cross sectional diameter ratio of the median nerve was measured. To measure the short-long diameter ratio, the long diameter (axis) was defined as the longest diameter of the median nerve, while the short diameter was defined as the longest diameter which was perpendicular to the long axis. The short diameter was divided by the long diameter to generate the ratio.

Figure 2. Mechanical Testing

a. The results of ultimate load

The ultimate load was greater in the dextrose injection groups, but the difference did not reach statistical significance ($P=0.08$).

b. The results of energy absorption

Same mark shows significant difference between each combination ($P<0.05$). There were significant increases in the 10% dextrose-double injection group than in the saline injection groups ($P<0.05$).

Figure 3. Mechanical Testing (Stiffness)

Significant difference between **1**: Saline-single and 10% dextrose-double

2: Saline-double and 10% dextrose-double, **3**: 10% dextrose-single and 10% dextrose-double, **4**: 20% dextrose-single and 10% dextrose-double ($P < 0.05$).

There were significant increases in the 10% dextrose-double injection group compared to the saline injection controls ($P < 0.05$).

Figure 4. Histology of Subsynovial Connective Tissue (x200)

The SSCT was irregular and thickened in the dextrose injection groups compared to the saline injection groups.

Figure 5. Subsynovial Connective Tissue Thickness

Same mark shows significant difference between each combination ($P < 0.05$). The thickness of the SSCT was significantly larger in the 10% dextrose-double injection group compared to the 10% saline-single injection group.

Figure 6. Nerve Short-Long Diameter Ratio

Identical marks indicate a significant differences ($P < 0.05$).

The nerve short-long diameter ratio was significantly lower in the dextrose injection groups than in the saline-single injection group ($P < 0.05$).