ORIGINAL RESEARCH

LONG TERM EFFECTS OF DEXTROSE PROLOTHERAPY FOR ANTERIOR CRUCIATE LIGAMENT LAXITY

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Context • *Use of dextrose prolotherapy. Prolotherapy is defined as injection that causes growth of normal cells or tissue.*
Objective • *Determine the 1 and 3 year efficacy of dextrose injection prolotherapy on anterior cruciate ligament (ACL) laxity. After year 1, determine patient tolerance of a stronger dextrose concentration (25% versus 10%).*
Design • *Prospective consecutive patient trial.*
Setting • *Outpatient physical medicine clinic.*
Patients or other participants • *Eighteen patients with 6 months or more of knee pain plus ACL knee laxity. This laxity was defined by a KT1000 anterior displacement difference (ADD) of 2 mm or more.*
Intervention • *Intraarticular injection of 6-9 cc of 10% dextrose at months 0, 2 ,4, 6, and 10. Injection with 6 cc of 25% dextrose at 12 months. Then, depending on patient preference, injection of either 10% or 25% dextrose every 2-4 months (based on patient preference) through 36 months.*
Main Outcome Measures • *Visual analogue scale (VAS) for pain at rest, pain on level surfaces, pain on stairs, and swelling. Goniometric flexion range of motion, and KT1000-measured ADD were also measured. All measurements were obtained at 0,6,12 and 36 months.*
Results • *Two patients did not reach 6 month data collection, 1 of whom was diagnosed with disseminated cancer. The second was wheelchair-bound and found long-distance travel to the clinic problematic. Sixteen subjects were available for data analysis. KT1000 ADD. measurement indicated that 6 knees measured as normal (not loose) after 6 months, 9 measured as normal after 1 year (6 injections), and 10 measured as normal at 3 years. At the 3 year follow-up, pain at rest, pain with walking, and pain with stair use had improved by 45%, 43% , and 35% respectively, Individual paired* t *tests indicated subjective swelling improved 63% (*P = *.017), flexion range of motion improved by 10.5 degrees (*P = *.002), and KT1000 ADD improved by 71% (*P = *.002). Eleven out of 16 patients preferred 10% dextrose injection.*
Conclusion • *In patients with symptomatic anterior cruciate ligament laxity, intermittent dextrose injection resulted in clinically and statistically significant improvement in ACL laxity, pain, swelling, and knee range of motion. (Altern Ther Health Med. 9(3):52-56)*

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Current treatment of anterior cruciate ligament (ACL) laxity involves strengthening of muscles about the knee to partially compensate for the ligament insufficiency. The only way to tighten an ACL ligament is to do so surgically. However, recurrence of laxity may occur even after surgery. The long period of activity modification and rehabilitation following ACL surgery is also a limitation. An injection method to create strengthening and tightening of the ACL ligament would be a valuable integrative medicine tool usable by general practitioners. If the solution used is inexpensive, as is the case with dextrose, third world applications would be substantial. Two previous studies demonstrated the potential for tightening of ACL ligament laxity via injection. These included a small study using injection of an inflammatory solution containing 1.25% phenol, 12.5% dextrose and 12.5% glycerin,[1] and a previous study by these authors using 10% dextrose.[2]

The current study is an expansion and extension of the previous 6-month, double-blind study by these authors, which was a study on osteoarthritis patients, some of whom had ACL laxity.[2] Thirteen patients in the original study met criteria for both osteoarthritis and ACL laxity, and 5 were not included since they did not meet x-ray criteria for osteoarthritis. All 18 patients were included in this study since they each met criteria for ACL laxity.

Our hypothesis was that ACL ligament laxity would stabilize or improve over a 36-month follow-up period with continued periodic (every 2-3 months) injection of dextrose. Ten percent dextrose was utilized in the first year of the current study since we wanted to demonstrate that dextrose can cause tightening of a ligament without inflammation. However, the concentration of dextrose commonly used for joint injection in osteoarthritis or ACL laxity is 25%. Tolerance of 25% dextrose injection, as compared to 10% dextrose injection, has not been determined in the literature, and for that reason we utilized 25% dextrose in those patients who preferred it after 1 year.

Prolotherapy is injection that causes growth of normal cells or tissue.[3] There are inflammatory methods of prolotherapy in which inflammation is briefly stimulated to create elevation of polypeptide growth factors.[4-6] This has sometimes been termed

sclerotherapy, but sclerotherapy is injection to create disorganized tissue for therapeutic reasons, not normal tissue. Examples of sclerotherapy include varicose leg vein sclerosis and esophageal sclerosis. Sclerotherapy is an inaccurate term to describe inflammatory prolotherapy in connective tissue, since biopsy studies have not shown disorganization after inflammatory solution injection in connective tissue with agents in current use.

There are also non-inflammatory varieties of prolotherapy such as direct injection of recombinant polypeptide growth factors, examples of which include injection of erythrocyte growth factor (EGF) for patients with anemia or patients expected to incur blood loss[7-8] and injection of colony stimulating factor (CSF) for patients with leukemia with loss of white blood cells.[9-10]

Human cells normally produce growth factors themselves, and can be stimulated to produce enough growth factors to begin proliferation. Dextrose exposure to human cells, including renal cortical fibroblasts and periodontal fibroblasts, elevates polypeptide growth factors by these cells within minutes to hours after injection, and has been shown to cause cell multiplication and matrix formation.[11-17] Our premise was that ACL ligament fibroblasts would proliferate in response to in vivo exposure to dextrose via intraarticular injection, resulting in tightening of loose ACL ligaments in patients with symptomatic ACL laxity.

METHODS

Our primary objective was to study the long term effect of a non-inflammatory (10%) concentration of dextrose (D-glucose in water) on patients with ACL laxity. Subjective variables included knee pain at rest, knee pain with walking, knee pain with stair use, and perceived knee swelling (100 mm visual analogue scales [VAS]). Objective measures included goniometrically-measured knee flexion range and KT-1000 measured knee laxity.

To determine ACL laxity clinically an anterior drawer test is performed. This displaces the lower leg anteriorly in relation to the femur and is a gross measurement, subject to significant human error. An electroarthrometer is used in orthopedic and sports medicine clinics to obtain an objective measurement of ACL laxity and to follow patients after surgery to determine if laxity is recurring. This machine measures the exact force applied and the millimeters of anterior displacement of the knee with the anterior drawer test maneuver performed at a fixed knee flexion angle. Since patients vary in the amount of soft tissue resistance and natural laxity, both knees of each patient must be tested. The difference between the values for each knee (anterior displacement difference or ADD) is a reliable measure of ACL laxity. The KT-1000 (Medmetric Corporation, San Diego, CA) is a well-accepted arthrometer in common use.[18-24] Daniel, in a study of 120 subjects without ACL laxity measured with 20 pound force, found that 88 percent of patients without ACL laxity had an ADD <2 mm .[21] Wroble reported that 90% of normal subjects had a KT1000 <2 mm. [24]

As new collagen matures, water loss occurs. This natural dehydration is accompanied by shrinkage end to end of the immature collagen, resulting in a tightening effect. This tightening effect cannot occur if the ligament has been completely ruptured. MRI scanning was not available to rule out complete ACL tear. Although using a threshold KT1000 ADD value of 3 mm instead of 2 mm would eliminate even more normal knees from the study group, to do so would have included excess numbers of patients with complete ACL tear.[21,23]

A reasonable summary of literature would be that use of a 2 mm ADD by KT-1000 to diagnose ACL laxity provides at least 85% sensitivity and 85% specificity.

With respect to determining flexion range of motion of knees, the method for goniometric range evaluation was as described in a recent physical medicine and rehabilitation text.[25]

Subjects were recruited from those that responded to an advertisement for patients with osteoarthritis of the knee. Eighteen patients met clinical criteria for anterior cruciate ligament laxity. All 18 received dextrose injections and were seen for data collection at the same intervals.

Patients who were taking glucosamine/chondroitin sulfate were asked to discontinue use due to a potential contributory action. Patients were allowed to continue NSAIDs, acetaminophen, occasional narcotics, calcium, and multivitamins.

At 12-month follow-up, patients received 25% dextrose injection instead of 10%, and were asked at next follow-up time (2-4 months later) if they preferred the 25% dextrose or preferred to return to 10% concentration. Injections after 1 year were given every 2-4 months as circumstances dictated, averaged every 2.9 months, and utilized the solution of preference.

The volume of solution utilized depended on patient perception of fullness. If the fullness sensation became uncomfortable for the patient at 6 cc, no further volume was injected.

Human subject research approval and monitoring was by the Institutional Review Committee of Bethany Medical Center in Kansas City, Kansas. Procedures followed were in accordance with ethical standards outlined in the Helsinki Declaration Revision of 1983. The statistical analysis software was Statistical Program for Social Science (SPSS) version 7.5 (manufactured by SPSS, Inc, Chicago, Ill.) Percentage improvement was calculated in the following manner: The value of each variable at time 0 was subtracted from the corresponding value at 12 and 36 months; this difference was divided by the value at time 0 and multiplied by 100. Hotelling multivariate analysis of paired observations for the data observed at 0 months and at follow-up was conducted, including pain at rest, pain with walking, pain with stair use, subjective swelling, goniometric flexion range, and KT1000 ADD.

RESULTS

The average ACL laxity patient was 68 years of age and weighed 182 pounds. Follow-up to the 3-year endpoint was good. Eighteen patients began the study. Two dropped out before first data collection (6 months), 1 of whom had disseminated cancer and the other long-distance transportation limitations. The remaining 16 patients were seen for at least a year, and 14 of these

were seen for a full 3 years. One dropped out, saying he was doing much better and did not need to come in, and the other patient indicated she had other health issues that prevented follow-up. An intention to treat approach to data analysis was taken, in that data from the last follow-up was included in the final analysis. The final analysis included 3-year data from 14 patients and 1-year data from 2 patients that dropped out early.

COMPLICATIONS AND SAFETY ISSUES

Discomfort after injection was minimal with some patients reporting a joint fullness and stiffness for several days. No allergic reactions or infections were noted.

1-Year Data

Hotelling multivariate analysis of paired observations for data observed at 0 and 12 months demonstrated a statistically significant difference between 0 and 12 months (P=.003). The results of individual paired t tests for the variables measured at 0 and 12 months is shown in Table 1. Of particular interest are the 2 objective variables, namely knee flexion, with improvement of 14 degrees in range of motion (P=.001) and KT1000 A.D.D. which improved 55% (P=.023). By 1 year 9/16 knees were no longer lax by machine measurement (ADD < 2 mm).

3-Year Data

Hotelling multivariate analysis of paired observations for the data observed at 0 and 36 months demonstrated a significant difference between 0 and 36 months (P=.014). The result of individual paired t tests for the variables measured at 0 and 36 months is shown in Table 2. Knee flexion was still 10.5 degrees better than at study onset (P=.002), and KT 1000 ADD had improved a total of 72% by then (P=.002). By 3 years, 10/16 knees were no longer lax by machine measurement.

Figure 1 illustrates the percentage improvement over time of pain with walking, subjective swelling and ADD by KT-1000.

Preference of Low (10%) versus High (25%) dextrose concentration:

Of the sixteen patients who received 25% dextrose injection at 1 year, 11 preferred the 10% solution, and 5 preferred the 25% solution. Several patients given 25% dextrose had a flare of joint pain sufficient to receive an intraarticular steroid injection prior to dropping concentration back to 10%.

DISCUSSION

This study indicates that tightening of a loose ligament by 10% dextrose injection is feasible. This complements studies of 10% dextrose effects on large and small joint arthritic joint injection with 10% dextrose which showed statistically significant benefit as well.[2,26] Although much more needs to be understood about optimum combinations of growth factors, some growth factors found to be elevated in human ligaments after injury include PDGF, TGF-β, EGF, bFGF, and IGF.[27] Since growth factors work together, the ability to keep a variety of growth factor levels high in an area may ultimately depend on innovative methods, such as infecting a human ligament or cartilage cell with a virus that produces such growth factors,[28] or by directly injecting genes without use of viruses.[29] However, simpler and inexpensive means to raise growth factor (cytokine) levels may play a role in the future as well. In vitro exposure of human cells to extracellular dextrose concentrations as little as 0.5% (normal intracellular concentration approximates 0.1%) results in an induction (activation) of 15 different gene segments within minutes to hours of cellular exposure. These gene segments include

TABLE 1 Results at 0 and 12 months for knees with ACL laxity (N = 16)

Characteristic	Mean & (SD)* 0 Months	Mean & (SD)* 12 Months	Mean Difference 0-12 Months	Standard Error of Mean Difference	95% CI† for the Mean Difference	Significance Between Means at 0 & 12 Months
Pain at rest	2.31 (2.41)	1.56 (2.10)	–.75	.41	–1.63 to +.131	.090
Pain with walking	4.19 (2.81)	2.50 (2.68)	–1.69	.49	–2.73 to –.65	.004
Pain with Stair Use	5.88 (3.24)	4.06 (3.17)	–1.82	.71	–3.32 to –.30	.022
Swelling	2.75 (2.96)	1.31 (2.24)	–1.44	.71	–2.94 to +.07	.060
Flexion Range	111.88(15.92)	125.94(6.78)	+14.06	3.35	+6.92 to + 21.21	.001
KT1000 ADD	2.88 (1.26)	1.32 (2.09)	–1.56	.62	–2.88 to –.24	.023

*SD, Standard Deviation; †CI, Confidence Interval

TABLE 2 Results at 0 and 36 months for knees with ACL laxity (N = 16)

Characteristic	Mean & (SD)* 0 months	Mean & (SD)* 36 months	Mean Difference 0-36 months	Standard Error of Mean Difference	95% CI† for the Mean Difference	Significance Between Means at 0 & 36 Months
Pain at rest	2.31 (2.41)	1.25 (2.32)	–1.06	.58	–2.30 to +.18	.087
Pain with walking	4.19 (2.81)	2.38 (2.25)	–1.81	.49	–2.85 to –.78	.002
Pain with Stair Use	5.88 (3.24)	3.82 (3.31)	–2.06	.66	–3.46 to –.67	.007
Swelling	2.75 (2.96)	1.00 (1.79)	–1.75	.65	–3.1 to –.37	.017
Flexion Range	111.88(15.92)	122.38(9.00)	+10.5	2.79	+4.56 to +16.44	.002
KT1000 ADD	2.88 (1.26)	.82 (2.04)	–2.06	.57	–3.27 to –.86	.002

*SD, Standard Deviation; †CI, Confidence Interval

those responsible for producing key growth factors.[17,30] Each type of cell response to dextrose is unique, but thus far dextrose has been found to raise the level of all of the growth factors identified with ligaments, including CTGF, and dextrose exposure has been shown to cause collagen synthesis in renal cortical fibroblasts and definite fibroblast proliferation.[11-16, 31]

This study suggests that 25% dextrose may not be the ideal solution for knee injection, as most patients preferred 10% dextrose. Inflammation, although brief with 25% dextrose injection, may elevate the level of disrepair factors such as interleukin-1 and tumor necrosis factor (TNF). These disrepair factors may bind or block growth factors.[32-33] In clinical practice, the predominant opinion is that 25% dextrose injection is more effective than 10% dextrose for intraarticular injection in arthritis. Whether it is or not may depend on the level of disrepair factors in the joint at the time of injection. It is of interest that disrepair factors may be blocked as well. Interleukin-1 receptor antagonist and TNF-1 receptor antagonist are in clinical use.[34-35] Use of such agents to block disrepair, while at the same time inducing a rise in growth factors, may be a future approach with more efficacy in soft tissue repair and arthritis treatment.

CONCLUSION

Dextrose injection prolotherapy at 2-3 month intervals resulted in elimination of laxity by machine measure in 10/16 knees in the study population, with statistically significant laxity improvement by 6 injections, sustainable through 3 years with periodic injection. Tightening of loose ligament structure is made possible by loss of water from maturing collagen, causing an end-to-end shortening. Given in vitro effects of dextrose on human cell growth and collagen production, it is likely that the mechanism of action of dextrose in this study was growth factor elevation. If financially feasible, future studies may consider measurement of growth factor levels in the knee after dextrose injection to determine if the same growth factors elevate in vivo as have been demonstrated to rise in vitro. In addition, injecting only the loose knee would be better than treating a population of osteoarthritic patients who request both knees to be injected (as was the case in this study). Clearly an improvement in side-to-side difference is easier to show if only 1 knee is treated. Potential applications for intraarticular dextrose injection could be considerable. These could include such things as preventing a return to ACL laxity after reconstructive surgery, prophylactic use in athletes to prevent ACL rupture, or use in non-candidates for surgery.

Acknowledgment

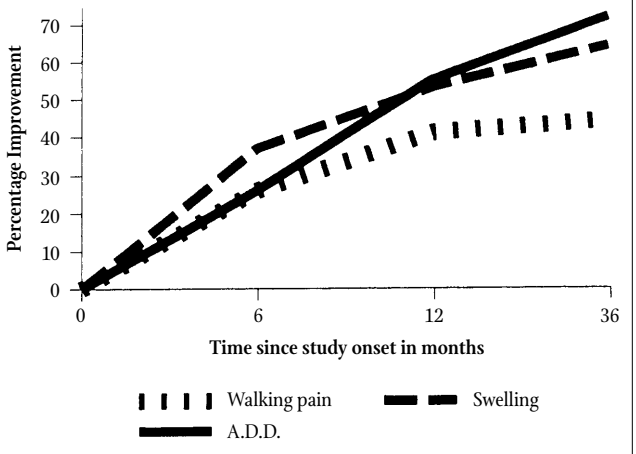

FIGURE Percentage improvement in walking pain, swelling, and ADD (machine measured laxity) over time

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