Biochemical injection treatment for discogenic low back pain

Robert G. Klein, M.D., - corresponding author
Pain Management Institute.
2927 De La Vina, Ste D
Santa Barbara, CA. 93105
Phone: 805 569-3169
Fax: 805 569-5670
E-mail: **RKlein42@aol.com**

Björn Eek, M.D.
Pain Management Institute, Spinal Diagnostics & Treatment Center

Conor O'Neill, M.D.
Spinal Diagnostics & Treatment Center

Caren Elin, D.C.,

Vert Mooney, M.D.
US Spine & Sport.

Richard Derby, M.D.
Spinal Diagnostics & Treatment Center.

Abstract:

Background context

Biochemical treatment options including attempts at intervertebral disc restoration are desirable for the physiologic treatment of degenerative disc disease.

Purpose

This was a pilot study to test the effectiveness of intra-discal injection therapy using agents known to induce proteoglycan synthesis in the treatment of intervertebral disc disease.

Study design

Prospective, within subject, experimental design was applied in the study.

Patient sample

Thirty patients, average age 46.5, with chronic intractable low back pain of 8.5 years average duration took part in the study. All patients had lumbar discography with reproduction of pain.

Outcome measures

Pre-treatment Roland-Morris disability scores and visual analogue scores were compared to one-year follow-up post-test values of these scores.

Methods

Lumbar intervertebral disks were injected with a solution of glucosamine and chondroitin sulfate combined with hypertonic dextrose and dimethlysulfoxide (DMSO). Assessment of pain and disability was completed before treatment and an average of 12 months after the last treatment.

Results

Post treatment Roland-Morris scores of 6.4±.994 were significantly ($p<.001$) lower than pre-treatment scores of 12.0 ±. 92 (mean± S.E). The post treatment visual analogue scores of 3.00±. 44 were also significantly less than the pre-treatment of 6.11± .33 (mean± S.E.). There were no complications or serious side effects, although post injection pain was moderate to severe for 48-72 hours and required epidural steroids in 5 cases.

Conclusions

Pain associated with intervertebral disc disease can effectively be treated in selected patients with injections of glucosamine, chondroitin sulfate, hypertonic dextrose, and (DMSO).

Keywords: low back pain, intervertebral disc, zygapophyseal joint, injection, glucosamine, chondroitin sulfate, dextrose, DMSO.

Introduction

Chronic low back pain represents a major burden to society and to the individuals afflicted with this common condition. Despite the existence of sophisticated diagnostic tools a specific diagnosis is often elusive, and the choice of appropriate treatment remains largely empiric. Pathology within the intervertebral disc and zygapophyseal joint plays a major role in nonspecific low back pain syndromes [1-5]. The treatment of the intervertebral disc portion of the pain is difficult and controversial, and many patients with chronic intractable pain ultimately require lumbar fusion surgery after the failure of conservative treatments.

The intervertebral disc is a complex anatomic and biochemical structure composed primarily of fibrocytes and chondrocytes in an avascular macromolecular matrix of collagen and proteoglycans [6]. The degenerative processes associated with injury and aging result in biochemical and morphological alterations of the disc. Morphological changes of dehydration, fissuring, and tearing of the nucleus, annulus and endplates are associated with molecular changes of decreased diffusion, decreased cell viability, decreased proteoglycan synthesis and alterations in collagen distribution [6-9].

Oral glucosamine and chondroitin sulfate, which enhance proteoglycan synthesis, have been used in multiple clinical trials and have generally been found to be effective and safe in the treatment of osteoarthritis of peripheral joints [10-14]. There is evidence that glucosamine and chondroitin sulfate synergistically enhance the natural hypermetabolic repair response of chondrocytes and retard the enzymatic degradation of cartilage [15]. This encouraged us to explore their potential use in degenerative disc disease.

Because the blood supply to the intervertebral disc is poor, and oral glucosamine and oral chondroitin sulfate do not clearly benefit patients with low back pain, [12] we elected to perform a pilot study using intra-discal injectable glucosamine and chondroitin sulfate combined empirically with other agents (DMSO and hypertonic dextrose) in an attempt to promote a reparative response in the intervertebral disc.

Methods

Patient selection and follow-up: Thirty patients participated in the study. These were all adult patients with chronic low back pain who failed to respond or responded poorly to a variety of previous methods of treatment including physical therapy, multiple analgesics, ligament prolotherapy, laminectomies, fusions, and IDET (intradiscal electrothermal annuloplasty) procedures and were being considered for additional surgical procedures. All of them had positive discography at one or more lumbar levels as evidenced by concordant pain provocation combined with morphologic disc abnormalities. Twenty-four of the thirty patients had involvement of 2 or more discs. Seven of the 30 patients had previously received the IDET treatment to a single disc with varying but generally poor responses. Six of these seven received treatment to the same disc previously treated by IDET, and one patient received treatment to a different disc. Three patients had prior lumbar fusions at a single level and were symptomatic at additional levels, and an additional three patients had laminectomies with persistent pain. Twenty-nine of the 30 patients had received previous prolotherapy treatments [16-17] to the low back ligaments with limited or no improvement. Four patients, two of whom had a prior lumbar fusion, were disabled and had been incapacitated for more than one year. The current data represents a minimum of 12 months and a maximum of 20 months of follow-up from the time of initiation of therapy.

Composition of injected solutions: A compounding pharmacist using sterile technique and USP grade pharmaceuticals prepared the solutions. The "disc solution" consisted of 0.5% chondroitin sulfate, 20% glucosamine hydrochloride, 12% DMSO and 2% Marcaine. These concentrations were derived based upon solubility and tolerance characteristics of the constituents. This was mixed with 1/3 non-ionic contrast and 1/3 of 50% dextrose at the time of injection. A total of 1-2 cc of the "resulting solution" was injected into each involved disc. If any leakage of contrast was noted into the epidural space the injection was terminated. The same solution without chondroitin was used to inject the zygapophyseal joints at all treated disc levels and was mixed with equal amounts of 50% dextrose prior to injection. The chondroitin was omitted from the zygapophyseal injections since previous testing of this solution intra-articularly proved it to be highly irritating to some of the patients. The zygapophyseal joint injection was performed after fluoroscopic confirmation of correct needle placement using intra-articular contrast.

Injection protocol: In order to avoid discomfort to the patient, the first series of injections was performed at the time of diagnostic discography. An intradiscal injection of 1-2cc of the "resulting solution" was utilized at each involved disc level as determined by discography. This was combined with injection of the zygapophyseal joints at the painful disc level(s) with the same solution, but without the added chondroitin sulfate. The injections were performed using fluoroscopic guidance by anesthesiologists and radiologists with extensive prior experience. Prophylactic antibiotics and standard discographic monitoring and sedation procedures were used for all the injections. Each patient was treated a maximum of 4 times at intervals of 2 or more months. All patients were informed as to the experimental nature of the study and of the potential risks as well as the potential benefits of participation, and all patients signed an informed consent.

Other treatments: Patients were allowed to continue their ongoing treatment protocols and pain medications as needed. Five patients required epidural injections of corticosteroids one to three weeks after receiving the intradiscal injections due to a significant flare-up of pain. One patient received oral corticosteroids for one week following an intra-discal injection. The use of the steroids significantly reduced the pain in all cases in which they were used.

Monitoring for toxicity: Patients were questioned regarding any adverse reactions to the treatment. No blood tests or other specific monitoring was performed.

Assessment of outcome: The success of any treatment for low back pain must rest on the patient's subjective assessment of pain and disability. We used a previously validated disability questionnaire designed by Roland, consisting of 24 questions pertaining to activities of daily living [18]. A score of 0 corresponded to no impact of low back pain on activities of daily living, and a score of 24 indicated an extreme level of dysfunction. Adding up the number of positive responses prior to treatment and comparing this with the post-treatment total determined the pre and post-treatment disability score. A standard visual analogue pain scale (0-10) was used to determine the patient's subjective estimate of pain pre and post treatment. Statistical analysis was performed using a paired 2-sample t test for the difference between means.

Results

A total of 20 women and 10 men entered the study. The average age was 46.5 years (range 27-62) and the average duration of pain was 8.5 years (range 1-20). The minimum duration of follow-up was 12 months (average 13 months). The average number of treatments was 2.5 (range 1-4) and the average number of discs treated was 2 (range 1-4). The results of the pre and post-treatment subjective disability and visual analogue pain scores are shown in Table 1. There was a statistically significant improvement in disability and pain scores with approximately a 50% improvement overall in both the pain and disability scores. Seventeen patients (57%) improved a minimum of 50% in either disability (average improvement 72%) or visual analogue scores (average improvement 76%).

The data shown in table 2 represent individual scores for each patient. The first seventeen patients listed had improvement in disability or visual analogue pain scores of a minimum of 50% and were considered good-excellent responders. The final 13 patients were considered poor responders.

Complications and side effects: All 30 patients experienced varying degrees of post injection pain. In most cases this could be controlled with oral analgesics and was limited to 72 hours of moderate to severe pain. One patient required a tapering dose of oral corticosteroids for one-week post treatment and 5 patients required epidural corticosteroids due to temporary exacerbations of pain. All patients were treated prophylactically with antibiotics at the time of each intra-discal injection, and there were no instances of disc space infection or other serious complications. There were no instances of skin rashes, systemic reactions, hypotension, or allergic reactions noted with any of the injections. One patient developed increased leg pains for 2 months after the procedure, which completely resolved.

Non-responders: There were a total of 13 patients who responded minimally with average improvements in visual analogue scores of 14% and disability scores of 8%. One patient (JC) had fibromyalgia syndrome with generalized musculoskeletal symptoms and responded poorly to 2 intra-discal injection treatments. One patient (JR) who failed to respond had advanced three level degenerative disc disease and spinal stenosis accompanied by bilateral straight leg raise limitation to 30 degrees and marked limitation of all lumbar movements. He had failed to respond to a previous laminectomy and foraminotomy. Two patients, both of whom received previous IDET therapy (RH, GG), elected to have spinal fusions after 3 months of failure to improve following a single intra-discal injection treatment. Two patients with previous lumbar spinal fusions, tissue hypersensitivity to palpation, and limitations of straight leg raising to 50 degrees or less bilaterally failed to respond.

Excellent and good response: Seventeen patients were judged to have a good or excellent response by virtue of an improvement in disability and/or visual analogue pain scores of at least 50%. Dramatic improvements occurred in many of these patients with an average reduction in the disability score of 72% and an average reduction of the visual analogue pain score of 76%. The response to treatment was gradual in all patients, but all responders had significant improvements after the first treatment whereas non-responders failed to show significant improvements with the first or subsequent treatments. Three of the 7 patients with prior IDET procedures were in the excellent response group and four were in the non-responder group although one of these (RH) was not treated at his previous L4-5 IDET level since he refused a repeat discogram at this level and only received one treatment at L5-S1 where the discogram was positive.

Discussion

The similarity between the arthritic peripheral joint and the degenerated intervertebral disc encouraged us to explore the potential use of glucosamine and chondroitin sulfate as biochemical agents that might facilitate the healing response. Our results showing statistically significant improvements in pain and disability in a group of patients, who were selected because of multi-level involvement and refractory pain, suggest that this is an approach worthy of further pursuit and refinement. The results of the present study compare favorably with Karasek's 12-month follow-up of patients treated with the IDET procedure [19]. In that study 35 patients with a single disc level of involvement were treated whereas our patients had multi-level involvement in 24 of the 30 cases, and an average of 2 levels were treated in our study. Sixty percent of Karasek's patients achieved at least a 50% reduction of their visual analogue pain scores compared to 57% in our series who had a minimum 50% reduction in pain and/or disability scores.

Studies have emerged over the past decade documenting the safety and efficacy of glucosamine and chondroitin sulfate, which act as essential substrates and contribute to the biosynthesis of proteoglycans [10-15]. Proteoglycans and collagens constitute the two major classes of macromolecules in the nucleus pulposus, annulus fibrosus, and hyaline cartilage end plate. Although cells are necessary to control the growth and repair of the disc, its mechanical function is determined largely by the properties of the extracellular matrix [20]. The proteoglycans consist of sulfated glycosaminoglycan side chains of chondroitin and keratan sulfate and hyaluronate bound to a protein core. Glucosamine sulfate forms half of the disaccharide subunit of keratan sulfate and of hyaluronic acid, which forms the backbone of proteoglycans aggregates in the intervertebral disc and in articular cartilage. Chondroitin sulfate is one of the predominant glycosoaminoglycans in articular cartilage as well as in the intervertebral disc [20].

We identified a group of patients with chronic low back pain of more than 8 years average duration in whom the intervertebral disc was the likely primary pain generator. We utilized intradiscal injections of glucosamine and chondroitin sulfate with the intention of enhancing proteoglycan synthesis. This was coupled with an attempt to induce growth factor release promoted by the use of hypertonic dextrose. Elevation of extracellular glucose to as little as .5% has been shown to raise levels of IGF-1 and IGF-2 in human mesangial cells, [21] TGF-Beta-1 in human mononuclear cells, [22] bFGF in human gingival fibroblasts [23], and platelet derived growth factor in human mesangial cells [24].

Research using growth factors has led to the repair of full thickness cartilage lesions in small animals, and studies of the canine intervertebral disc suggest that growth factors may be useful in modulating the repair of the nucleus and transition zone [25-27]. A single injection of TGF-beta has been shown to induce 3 weeks of proteoglycans synthesis [28].

This suggests that continuous exposure to growth factors may not be necessary for healing of joints (or discs) to occur. DNA levels for growth factor production increase within hours after cellular exposure to elevated glucose concentrations [29]. There may be elevated levels of metalloproteinases and other degradative enzymes in degenerative disc disease and in established cases of osteoarthritis that may block the effect of a single growth factor. The potential combination of multiple agents and the release of multiple growth factors may be necessary to overcome this inhibition. Glucose in addition to raising multiple growth factors has also been found to suppress potential disrepair factors including interleukins such as IL-2, IL-6 and IL-10 [22]. The exposure of cells to hyperosmolar solutions with changes in osmolarity of as little as 50 mOsm activates kinases, which also may have an effect on growth factor regulation [27, 30].

DMSO was added to the injected solution to enhance diffusion of the dextrose, glucosamine, and chondroitin throughout the full extent of the disc. Studies in rabbits with degenerative disc disease indicate that DMSO is necessary to allow a methylene blue carrier to penetrate the full extent of the disc (Vert Mooney, M.D., unpublished data, Feb. 2001). It also appears to have potent free radical scavenging properties that may be useful in the setting of chronic pain and tissue hypoxia [31]. DMSO is FDA approved for treatment of interstitial cystitis and is available in pure form.

The patients in our study generally responded slowly to the intra-discal treatment, consistent with a biologic rather than an analgesic response. Typically, three or more months were required to appreciate the full extent of improvement from each treatment. Despite the selection process (which insured the inclusion of only the most treatment refractory patients with chronic pain), there was improvement that was statistically significant. Three of the six patients previously treated unsuccessfully with the IDET procedure subsequently responded favorably to the disc and apophyseal injections. The longest follow-up in our series is 20 months and there has been no decay of the positive response.

Based on our initial experience future studies would exclude patients with prior fusions or long term disability, and we would exclude patients who demonstrate bilateral limitations of the straight leg raise test to less than 50 degrees. We would also exclude patients who demonstrate extreme tissue hypersensitivity to palpation, which usually corresponds with chemically sensitive discs with discographic induction of pain at less than 30psi. These patients may become candidates for intradiscal injection treatment after initial radiofrequency treatments or corticosteroid injections render the disc less sensitive. Prophylactic epidural injections of corticosteroids may also be considered in future studies to diminish the post injection flare-up of pain that occurred in most patients in our series and was severe enough in 6 of the 30 cases to require epidural or systemic corticosteroids.

The present pilot study was neither blinded nor randomized, and we cannot rule out a placebo effect as a major contributor to the improvement. It is unlikely that this population of patients with chronic refractory pain would achieve spontaneous and sustained improvements of their pain [32]. These patients were evaluated before and after treatment using standardized outcome methods, and co-interventions were kept to a minimum. Based on our results this treatment approach is feasible, appears to have a low profile of side effects, and may avoid more costly surgical and other invasive procedures. It may also be useful in cases where the IDET or similar procedures has failed to achieve a satisfactory response.

We hypothesize that the reductions in pain and disability seen in this study are due to favorable alterations in the biochemical milieu of the intervertebral disc and apophyseal joints, but we have no direct proof that this is the case, and further studies including serial MRI scans are clearly needed to address this important question.

Based upon clinical presentation and discography the primary source of pain in the patients in our study was the disc pathology. However, we elected to also empirically treat the zygapophyseal joints at the affected disc levels. The relative contribution of the intervertebral disc and zygapophyseal joints to the total burden of chronic low back pain in individual patients is debatable. There are studies that suggest a causal relationship between disc degeneration and osteoarthritis in the facet joints, and in most cases the severity of the osteoarthritis correlates with the extent of disc degeneration [9]. Other studies suggest that in patients with chronic low back pain the combination of discogenic pain and zygapophyseal joint pain is uncommon, and that the concept of the three joint complex may be pathologically correct but not clinically relevant in the majority of cases [5]. As both the discs and facet joints were treated in all individuals, we cannot exclude the possibility that some patients responded in part, or even wholly, as a result of the facet injections. Future studies will need to address the relative importance of injecting each of these structures.

The potential to treat a damaged motion segment in a more physiological manner using glucosamine, chondroitin sulfate, dextrose, and DMSO needs to be further explored since there are a large number of patients who could benefit from this approach. Even patients with multilevel involvement who are not suitable operative or IDET candidates can be treated. The concentrations and composition of the solutions putatively used for biologic tissue repair will need further study and refinement as experience accumulates with a larger and more varied patient database. Ideally, each component of the injection solution should be tested independently to determine optimal combinations and concentrations, but this was not practical in a private practice setting and with a pilot study. A double blind study would also be desirable to test this injection approach, but this would prove difficult in view of the temporary pain induced post treatment in all cases, which would make blinding impossible. Additionally, the use of fluoroscopic x-rays in a placebo group could not be justified. A study in which patients are randomized to receive intra-discal injection therapy or the IDET or a similar comparison procedure would be worthwhile.

Diwan has recently reviewed the topic of intervertebral disc replacement therapy as well as the potential for disc regeneration using a variety of growth factors. The possible role of human osteogenic protein-1 (rhOP-1) is especially relevant in that it appears to stimulate the metabolism of the nucleus pulposus and the annulus fibrosus suggesting its potential use in promoting synthesis and repair of matrix in degenerating discs. [33] Ideally, specific growth factors, once they are isolated and tested, can be used to stimulate chondrocytes and fibroblasts to induce a healing response. Until these growth factors become available the best option is to use indirect stimulants that promote connective tissue healing.

Conclusions: Intradiscal injections of a glucosamine and chondroitin sulfate solution combined with dextrose and dimethylsulfoxide may provoke indirect stimulation of connective tissue healing. The use of these injections combined with zygapophyseal injections resulted in a significant decrease in pain and disability in patients with refractory chronic low back pain.

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Table 1 Averaged scores in all 30 patients

	Pre-treatment	Post-treatment	p value
Disability score Mean ± S.E.	12.0± .925	6.4± .994	<.001
Visual analogue score Mean± S.E.	6.11± .332	3.00± .441	<.001

Table 2 Data for each patient.

Patient	Age	Sex	Years of Pain	RM[1] Pre-treatment	RM Post-treatment	VA[2] Pre-treatment	VA Post-treatment	Number of treatments	Number of discs
LG	56	F	20	14	0	6.9	0	2	1
PC [3]	55	F	5	17	4	8	0	2	2
ME	40	F	15	17	0	10	0	3	2
RJ	56	M	1	19	1	6.2	0.2	3	3
MM[4]	38	F	11	16	6	7	3	4	2
KT[4]	51	F	5	20	14	7.5	3	4	2
CB	51	F	5	3	1	6.1	0	2	2
PT	41	M	5	7	3	4.5	2	3	2
ME[4]	51	F	8	7	2	4.3	2.5	4	2
JL	54	M	20	10	1	6	1	2	2
JP[3]	27	F	3	6	5	5.7	1.5	3	2
NB	58	F	5	15	2	3.5	0	2	2
CH	57	F	15	13	2	7.3	5	2	2
ML	38	F	2	9	6	7	3.2	3	2
CR	35	F	20	14	0	7.5	0.5	3	4
JM	58	F	15	8	1	2.3	0	3	2
DF	42	M	2	11	7	6.8	3.4	2	1
JR[3]	58	M	15	10	9	8.7	9	2	3
BK	49	F	10	7	7	4.6	5	3	2
BH	55	M	10	3	3	5.7	5	2	1
TR[4,5]	35	F	4	14	9	8.5	4.5	2	3
AD	52	F	10	4	4	3.4	3	3	2
KA[3]	25	F	7	16	13	5.5	2.9	3	2
JM[3,5]	38	M	6	20	20	6.3	6.5	2	3
GG[4]	51	F	5	13	13	3.3	3.3	1	1
JC	34	F	3	13	15	7.1	5	2	1
TH[5]	43	M	5	19	13	5	3.5	2	2
MJ[3,5]	34	F	10	16	12	8.5	7	3	2
RM[4]	52	M	7	7	7	4	4	2	2
RH[4]	62	M	5	12	12	6.1	6.1	1	1

[1] RM is the Roland-Morris disability score
[2] VA is the visual analog pain score
[3] Patients with prior laminectomy or fusion
[4] Patients with prior IDET treatments
[5] Patients with chronic disability