Chemonucleolysis in low back pain

Gül Köknel Talu M.D., Assoc. Prof.*, Richard Derby M.D.**

ÖZET

Bel ağrılarında kemonukleolizis

Rüptüre olan diskten kaynaklanan bel ağrısı genel olarak çözümlenmemiş bir problemdir. Birçok tedavi seçeneği geliştirilmiş ve denenmektedir, fakat uzun dönemde tatmin edici sonuçları çok düşüktür. Bununla birlikte çelişkili sonuçların en sık sebepleri, hasta seçiminin yetersizliği, amacından yoksun değerlendirme parametreleri, tanının güvenilmezliği ve çoğu kez kanıta dayanmayan özel tedavi yöntemlerinin uygulanması olarak sıralanabilir. Farklı yöntemler ile uygulanabilen kemonukleozis, konservatif tedavilerin etkisiz olduğu disk herniasyonlarına bağlı olan hem siyatik hem de bel ağrılarının tedavisinde basit ve maliyeti düşük cerrahi öncesi denenebilecek tedavi seçeneği olarak bildirilmektedir.

Anahtar Kelimeler: Bel ağrısı, kemonukleolizis, kimopapain, ozon enjeksiyonu, disk içi enjeksiyonlar.

ABSTRACT

Chemonucleolysis in low back pain

Low back pain caused by an internally disrupted disc is a universal unresolved problem. Many treatment options have been tried and many are in development, but few have satisfactory long-term results. Although the most often used excuse for inconsistent results is poor patient selection and the lack of objective evaluation parameters, the diagnosis is often elusive and definitive selection criteria for any specific treatment modality is usually unproven. Chemonucleolysis performed by various techniques, is a cost-effective and simple method for treating both low back pain and sciatica caused by herniated discs where conservative methods are ineffective. Here we discuss the techniques chemunucleslysin in lowback pain.

Key words: *Low back pain, Chemonucleolysis, ozone-disc injection, intradiscal injection, chimopapain.*

*Department of Algology, Medical Faculty of Istanbul University
**Spinal Diagnostics and Treatment Center, Daly City, California, USA.

Correspondence to:
Gül Köknel Talu MD., Assoc. Prof.*
Department of Algology, Medical Faculty of Istanbul University
Email: gktalu@yahoo.com

Introduction

Low back pain caused by an internally disrupted disc is a universal unresolved problem. Many treatment options have been tried and many are in development, but few have satisfactory long-term results and none are clearly superior or inferior to another more or less invasive treatments. Although the most often used excuse for inconsistent results is poor patient selection and the lack of objective evaluation parameters, the diagnosis is often elusive and definitive selection criteria for any specific treatment modality is usually unproven. Nevertheless, a common consequence of disc disruption is a herniated disc that can be easily visualized on an MRI scan.

Open microsurgical decompression is the gold standard for treating lumbar herniations larger than 5 mm causing neural compression and spinal stenosis. Quoted success rate are 90% with complication rates less than 2%. However, success rates are considerably lower when protrusions are smaller (Postacchini et al. 1998). In addition, many patients do not want to have open surgery and would prefer a less invasive percutaneous option. If the results are comparable to microdiscectomy, the potential for a less expensive, safer, and more convenient option would appeal to many patients.

Disc Herniation:

Neural compression causes paresthesias, weakness, and numbness, but not necessarily pain. Pain is caused by inflammation and edema caused by the exposure of the body to nuclear contents. Inflammatory enzymes are released by nuclear chondrocytes and blood born histiocytes that accumulated in response to the presence of the heretofore isolated nuclear contents. These inflammatory mediators are many and include tumor necrosis factor, phospholipase A2, leukotriens, protaglandins, substance P, and gene related peptide. They not only cause sensitization of the abundant periannular mechanical receptors, nocioceptors, and sympathetic afferent fibers, but injure and kill nerve fibers. In an attempt to reabsorb the foreign material , blood vessels accompanied by small nerve fibers invade the annulus and give access to inflammatory cells (Koike 2003, Gangi 1998, Selby 1995, Kramis 1995, Kawami 1995, Smith 1964) resulting in an accelerated degeneration and disruption of the intervertebral disc. In many patients, the result is a prolonged course of unresolved low back and referred extremity pain.

Chemonucleolysis:

By definition, chemonucleolysis is the digestion and degradation of the nucleus pulposis by a chemical reaction that typically results from the interaction with a percuanteously injected substance. Theoretically, reduction in the size of the protrusion, decrease in nuclear pressure, reduced chemical sensitivity, or a combination of the former results in decreased pain.
Percutaneous access to the disc was first used in the 1950's as a needle biopsy technique (Craig 1955).

But dissolving nuclear protyoglcans by the injection of chymopapain was the first percutaneous technique used to treat radicular pain caused by a herniated nucleus purposes. Introduced in the 1960's by Lyman Smith (Lievseth 1999, Smith 1964, Smith 1963) chemonucleolysis with chymopapain is still used in many countries to treat radicular pain caused by herniated discs, but in the United States catastrophic complications following inadvertent injection of chymopapaine into the subarachnoid space damped the early enthusiasm for this procedure by week-end trained surgeons and prohibitive medical-legal barriers discouraged to its further use. Despite this fact, the procedure is inherently safe when performed by an experienced interventionalist In fact, compared to open discectomy, Hartz et al. (Hartz 2003) found 12 observational outcome studies and 6 RCTs outcome showing a comparable 93% success rate with longer follow-up data.

Although chymopapain is the most extensively used and researched chemonucleolysis method, other methods are being reseached and used. These methods include human cathepsin L, condroitinase ABC, collagenase and recently ozone-oxygen combination (Kim 2002, Wittenberg 2001).

Chemonucleolysis with chymopapain

Used less frequently today than 20 years ago, chymopapain remains the most commonly used chemonucleolysis method with the most reseach with the best outcome (Wittenberg 2001, Kubo 1999) Chymopapain reduces the water binding capacity of nucleus pulposus by degrading nuclear proteoglycans. Dehydration may relieve pa-

in by lowering nuclear pressure, mechanically shrinking the size of the protrusion, or destroying small nerve fibers (Sumida 1999, Lievseth 1999, Kiester 1994).

Since 1975, more than 16000 patients with sciatica have been treated chymopapain injection with reported "good and excellent" outcomes varying between 70-90% (Wittenberg 2001). One must however realize that the success rates are primarily based on relief of leg pain and not back pain. Initial animal studies indicated that following chymopapain injection the disc height would eventually recover (Hartz 2003, Kiester 1994), but Leiveth et al (Lieveth 1999) found that shortly after intranuclear chymopapain injection, disc heights decreased and there was no recovery at seven years follow-up. Even though disc heights are reduced, separate studies by Lu and Spencer (Lu 2004, Lu 1997, Spencer 1984) showed post treatment increased spinal flexibility in all motion planes. Whether increased flexibility is good or whether it is bad because it results in "instability" and back pain of back pain is unresolved.

Like all procedures, proper patient selection is important and include (Kim 2002) Using these criteria, in 2002 Kim et al quoted an 85% "success rate" after reviewing their 3000 patient case series. In addition, a 5 year prospective randomized trial by Wittenberg et al. (Wittenberg 2001) found chympapaine more effective than coloagenase.

Despite chymopapain's apparent effeacy for treating radicular pain cause by herniated disc, chympopapain has both minor and catastophic complications In addition to serious anaphylactic reactions, chymopapain is neurotoxic when directly injected into nerves of the subarrachnoid space (Moon et al. 1990). In animal studies, chymopapain causes adverse changes in the vertebral body and endplate resulting in endochondrial ossification and osteophyte formation In humans, there is a dose related decreased disc height, increase in radial disc bulging, and increased segmental motion (Kim 2002).

Chemonucleolysis with Ozone

An unstable allotropic form of oxygen, ozone, (O3, 48 Kdalton) has been used for many years for various medical conditions, but remains a controversial treatment option and has only gained wide-spread use in Italy. Its use to decompress herniated discs and to supposedly reduce epidural inflammation is a more recent use, but its theoretical mechanism of action are supported by some studies (Bocci 2002, Viebahn 1994).

Mechanism of action

Many potentiall beneficial effects have been attributed to ozone that include bactericidal, fungicidal, virustatic, immunomodulating, analgesic and anti-inflammatory actions. Oxygen-ozone therapy is administered in the form of an oxygen-ozone gas mixture ranging in concentrations of between 1-40 ugr/ml of Oxygen, but therapeutic concentration is 27ugr O3 per ml of Oxygen (Bocci 2002, Viebahn 1994).

Ozone causes oxidation of the unsaturated double bonds between the phospholipids and the lipoproteins causing denaturation of cell membrane proteins and the release of free radicals. Injected within the nucleus, free radicals may destroy both the glycoproteins responsible for disc hydration as well as the chondroctes that produce them. In therapeudic concentrations of 27 to 30 gr/ml, injection of ozone into rabbit discs cause interstitial edema with eosinophilic degeneration and shrinkage of the cell nucleus. In time, there is reduction in the number of chondrocytes and decreased disc volume. Other studies have substantiated these effects by showing a reduction in the herniation size (Bocci 2002, Iliakis 2001, sumida 1999, Viebahn 1994).

Summarized elsewhere, theoretical beneficial effects of therapeutic concentrations of Oxygen-ozone therapy include the following:

1. Increased tissue oxygenation resulting is more rapid revascularization resulting in a more rapid reabsorption of the herniated nucleus pulposis

2. Decreased proteinase release and increased release of immunosupressive cytokines

3. Decreased disc volume resulting from a decreased synthesis of proteoglycans and direct destruction of proteoglycans

4. Inhibition of inflammation (Andruela 2003, Iliakis 2001)

Patient selection criteria

Oxygen-ozone therapy has been used to treat patients with low back pain with or without radicular pain who have failed conservative treatment modalities like medical therapy, bed rest, physiotherapy. Relative contraindications include significant paresthesia, hypoesthesia, or any deg-

ree of muscle weakness. Imaging studies should show a small-medium size herniated disc that clinically correlates with the patients' symptoms. Although no studies compare clinical outcome for discogenic low back and pure versus radicular pain, similar to other treatments for herniated discs, one might expect ozone-oxygen is probably more effective for reducing radicular pain (Andruela 2003, Jeon 2003, Kim2002, Taylor 1990).

Technique

O2-O3 mixture with 27-30 micrograms/ml is administered intradiscally through a standard posterior-lateral appraoach to the intervertebral disc with a 25-22 guage needle and many physicians also inject the mixture within the foraminal epidural space. The rate of injection either into the disc nucleus or into the perineural tissues has not been clearly or consistently stated in prior reports, but the intradiscal volumes range from 4ml to 20ml (Andruela 2003, Iliakis 2001). Perhaps because of ozone's bactericide and antivirutic properties, prior reports have not indicated a prophylactic use of antibiotics.

Evidence

Ozone therapy for herniated discs remains understudied. In 2003 Kim et al. presented evidence that in rabbit discs injected ozone caused an effect similar to the chemonucleolytic effect caused by the injection of chymopapain (Kim et al. 2003). In five patients who failed ozone treatment and subsequently had microdiscectomy, the histological examination of the removed tissue showed disc dehydration with a fibrillary matrix of collagen fibers and vacuole formation within disc chondrocytes (Andruela 2003) On the other hand the same study found chondrocyte hyperplasia, proliferation and signs of red blood formation accompanied by lymphocyte inflammation in the histopathologic examination of herniated disc not treated with ozone (Iliakis 2001).

A recent retrospective audit by Muto et al. (Muto 2004) reported a 75% clinical "success" rate and a 63% "success" rate for CT scan reduction in disc herniation at 6 months. The authors reported no early or late complications in the 2200 patients (Muto 2004). In a similar study D'Erme et al. (D'Erme 1998) did a retrospective 3 month audit of 1000 patients treated with intradiscal ozone. They reported 68% positive results with no major side effects or complications. In 50 patients with post procedure CT scans the authors reported that 82% had a reduction in herniation size (D'Erme 1998).

In one of the few prospective study's, Kim et al. (Kim 2003) evaluated 62 patients with leg pain due to a disc herniation treated with the intranuclear injection of 20 ml of a 30ug/ml ozone solution. They reported an 84.8% "successful" outcome with the MRI visulized reduction in disc herniation size in 63.6% of the cases at six months (Kim 2003).

Only one comparative study and no controlled studies have been done. Andreula et al. (Andreula 2004) compared the clinical outcome following intradiscal and periganglionic ozone infiltration with intradiscal ozone and periganglionic steroid infiltration. The study revealed better results in the ozone and steroid combination group.

Although most studies evaluating the clinical efficacy of ozone are suspect, they do however include a large number of cases with reported favorable results ranging between 68% to 85% and favorable radiologic results between 68% and 85% More importantly, the treatment appears to be benign. No reports of serious complications have been reported with the exception of one case of an acute bilateral vitreo-retinal hemorrhage (Lo Guidice 2004). The amount injected and the exact location of the needle was not presented, but needle misplacement with intravenous or intra-arterial injection might best explain this rare complication.

Other agents

The intradiscal injection of cortico-steroids has been often used to treat back and radicular pain caused by intradiscal inflammation. Results have however not been consistent. A recent controlled study by Khot et al (Khot 2004) found no diffeence in outcome at one year in intadiscal saline compared to the intradiscal injection of corticosteroid (Khot 2004).

Temporary reduction in intradiscal pressure can be achieved by the injection of hypertonic saline into rabbit discs (Sato 2000) and the repetitive intradiscal injection of hypertonic saline may provide a more long lasting reduction of intradiscal pressure in rabbit discs (Sato2003, Sato 2002). The recent report of the clinical effectiveness of

a “restorative solution” containing 12.5% dextrose, glucosamine, and chondroitin sulphate (Derby et al. 2004, Klein’s et al. 2003), could be due to the pressure reduction caused by the hypertonic dextrose. In fact, Klein reported favorable outcome following the injection of 10% saline into patients discs (Klein et al. 2003).

Animal studies have shown proteolysis and a subsequent reduction in protein content following the injection of Chondroitinase ABC (C-ABC) into disc nucleus (Lu 1997). Injection of Chondroitinase into rabbits may also directly decrease colleganase and decrease the production of PGE2 and NO (Sakumo 2003). Ishikawa et al. (Ishikawa et. al. 1999) postulated that Chondroitinase found an enhanced resolution of epidurally implated nucleus pulposis in rabbits and postulated it was due to more easily infiltration of inflammatory cells, increased deoxyribonucleic acid content, decrease in chondroitin sulphate amount (Ishikawa et. al. 1999).

Collagenase has also been studied as a more benign cheonucleolysis treatment with fewer allergic reactions compared to chymopapain ane Chondroitinase ABC. In animal studies collagenase has no or very low allergic reactions. Prospectiely comparing the long-term effects of application of chymopapain and collagenase, Wittenberg found that only 28% of the treated patients required surgical intervention and the remaining patients had statistically similar good-excellent results reported to be 100% in the chymopapain group and 93% in the collagenase group. However, because nine patient’s treated with collagenase developed neurologic deficits, the author concluded that collagenase needs further study (Wittemnberg 2001).

Conclusion

Chemonucleolysis is a cost-effective and simple method for treating both low back pain and sciatica caused by herniated discs where conservative methods are ineffective. Although chymopapaine remains the best studied and only validated chemonucleolysis adgent, other cheaper and less hazardous methods such as ozone-oxygen or intradiscal hypertonic solutions should be more rigorously evaluated.

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