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Sciatica caused by disc herniation: Why is Chymopapain Chemonucleolysis denied to our patients?

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Abstract

Background

This study was undertaken to assess the long term outcome on the quality of life of patients with sciatica following treatment with chemonucleolysis, and to assess the complications.

Methods

This is a retrospective review carried out in a consecutive group of patients suffering from sciatica treated by chemonucleolysis. Patients were followed up by questionnaires to obtain Macnab score; satisfaction, SF 36, and case note review for complications and repeat spinal surgery.

Results

Six hundred and five patients (56% males, 44% females) treated over a ten year period from 1991 to 2000 were followed up. Average age was 47 years (range 17 - 88 years). The duration of symptoms prior to treatment averaged 10 months (range 1 - 20 months) and the herniation was confirmed by Myelogram (7%), CT Scan (34%), or MRI (59%). There were 578 single level and 27 double levels treated. Eighty five percent of herniations were typical single level, and 15% were atypical that is: patients with dominant back pain with sciatica, recurrent herniations following surgery at the same level, recurrent herniations at another level following chemonucleolysis, double levels treated patients with mainly neurological deficits and one cauda equina syndrome. Average follow up was 62 months (range 12 - 123) with a 78% satisfaction rate, with a 14% surgical intervention rate made up of 9% decompression, 1% repeat chemonucleolysis at another level and 4% fusion rate. SF-36 scores generally correlated with age and sex on scores for the normal local population.

Conclusions

This is a retrospective study and showed that chemonucleolysis was effective with a high satisfaction rate. It restores quality of life close to that expected in the population, and is safe with no complications related to the procedure. It is a cost effective daycare procedure with a lasting result.

KEYWORDS: CHYMOPAPAIN, CHEMONUCLEOLYSIS, SCIATICA, DISC HERNIAION, LUMBAR SPINE, BACK PAIN, COMPLICATIONS, LONG TERM FOLLOW UP, OUTCOME

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Introduction

Chymopapain chemonucleolysis was and is potentially an excellent method of treatment that is currently being denied to patients suffering from sciatica due to a soft disc herniation. Chymopapain chemonucleolysis was first reported by Lyman Smith in 1964 and the first product called Disease was manufactured by Smith Laboratories Inc. It became widely used throughout Europe, North America and Australia¹⁻¹⁶ and was demonstrated to be an effective and

safe method of treatment. The enzyme chymopapain is injected by the lateral route into the center of the nucleus with digestion of the proteoglycan of the nucleus and the herniation, the products being excreted in the urine.^{17,18,19} A purer preparation (Chymodiactin, Smith Laboratories Inc. USA) was later introduced due to a risk of anaphylaxis and its efficacy has been established in many randomized studies compared to a placebo;²⁰⁻²³ and to surgery.²⁴⁻²⁷ In 2001 two excellent review papers described the history and status of the procedure.^{28,29} Unfortunately the enzyme

ceased to be available in 2002 for non-scientific commercial reasons.

In 1995 Boots Pharmaceuticals, based in Nottingham, U. K. manufactured, owned and marketed the product. Their training and clinician support was second to none and uptake of the treatment in the United Kingdom was increasing by 30% annually. For financial reasons, they sold the pharmaceutical business to BASF, based in Germany, who decided to move the manufacture from Nottingham in the U. K. to Germany. In 2000, BASF then sold, part of their pharmaceutical business to Abbot Pharmaceuticals before the lab had transferred. Abbot consulted widely whether to proceed with the laboratory setup and in the end, decided not to go ahead. Eventually stocks of Chymodiactin ran out.

Open surgery (micro- or standard discectomy) to remove the herniation entrapping the nerve root, remains the treatment of choice, often with removal of much of the remaining nucleus.³⁰⁻³⁸ Excellent results can be achieved but it remains a major operative procedure with a risk of complications and recurrence.³⁹⁻⁴⁵ Attempts to reduce the risks have led to the development of less invasive techniques.⁴⁶⁻⁵¹ Sadly the least invasive technique of chymopapain chemonucleolysis, remains unavailable.

The author carried out over 2,000 chemonucleolysis procedures over a twenty year period, from 1982 to 2002. He introduced the procedure by means of a prospective randomized study of 100 consecutive patients with a follow up of one, 10-13, and 24-27 years demonstrating no difference in either the clinical or radiological outcomes.^{52,53} This paper reports the results of a consecutive cohort of patients over a ten year period (who would otherwise have been considered suitable for discectomy), treated by chymopapain chemonucleolysis. There was no selection based on age, size of herniation or level, but simply on the patient's symptoms of dominant leg pain, with or without neurological signs and demonstrated to be due to a herniated disc by an appropriate spinal investigation.

Material and Method

This is a retrospective review of six hundred and five patients treated by the author collated from a review of the operating lists during the period 1991 to 2000, and whose case notes were available for review. Patients were assessed according to the Macnab Criteria (Table 1). All patients had at least three months of non-operative care with analgesics, relative rest, and physiotherapy and if not significantly improved, they were offered chemonucleolysis. They had dominant leg pain with or without low back pain, restricted Straight leg raising and an investigation demonstrating a causative herniation. Having symptoms requiring surgery prior to chemonucleolysis, I believe that they are all classified as poor on Macnab Criteria. Complications and long term outcome including the impact of chemonucleolysis on quality of life of patients with sciatica were assessed. The case records were reviewed for details of presentation, past history of spinal treatments, radiological investigations, peri-operative and post operative complications and subsequent procedures if any. Patients were sent questionnaires to allow follow up assessment of Macnab Criteria, whether satisfied or not satisfied with treatment and an SF36 to allow comparison of Quality of life to the local norm.

Technique of Chemonucleolysis

All patients were offered active intervention if symptoms have not improved following an adequate period of conservative treatment of 6 - 12 weeks and were then listed for the procedure. During the years 2001 to 1995, patients had an overnight stay in Hospital, and from 1995 - 2000 the procedure was performed as a day case. Patients were admitted early in the morning. One hour before the procedure 10 -15 mg of Cyclimorph (morphine tartrate 10 or 15 mg with cyclizine tartrate 50mg/ml) was given by intramuscular injection depending on the patient's

Table 1. Macnab Criteria (Macnab I. "negative disc exploration: an analysis of the cause of nerve root involvement in sixtyeight patients." J Bone Joint Surg (Am) 1971;53:891-903).

- Excellent: No pain; no restriction of activity.
- Good: Occasional back or leg pain of sufficient severity to interfere with the patient's ability to do his normal work or his capacity to enjoy himself in his leisure hours.
- Fair: Improved functional capacity, but handicapped by intermittent pain of sufficient severity to curtail or modify work or leisure activities.
- Poor: No improvement or insufficient improvement to enable increase in activities; further operative intervention required.

weight. In the anaesthetic room, a large bore IV was inserted, and through this 2cc Midazolam hydrochloride was given as sedation and the patient, was positioned on the operating table, with a single arm image intensifier, positioned so that simply swinging it through 90 degrees gave a true AP and lateral view of the disc. Ten ml of bupivacaine was injected into the skin and muscle down to the disc. An 18 gauge needle passed down to the postero-lateral corner of the disc and then a 22 gage needle passed through it railroad fashion into the center of the nucleus. A discography was performed with a non-ionic contrast (Omnipaque 240 mgm/ml) by slow injection of 0.5cc to demonstrate the dye entering the disc (and often, the herniation). A small amount of propofol (Diprivan, AstraZeneca) was titrated via the IV, just enough to make the patient still, co-operative and amnesic, then one cc of Chymodiactin (2000 IU) was slowly injected. Patients always awoke rapidly and routine monitoring continued in the recovery room for two hours and discharged an hour or two later with a progress advice sheet. An assessment carried out in the recovery area within one hour of the procedure in 50 patients showed that 31 of them (60%) had complete or greatly reduced leg pain with a corresponding reduction in straight leg raising (unpublished data). The rest had moderate or no improvement at that time point.

Results

Review of the case records

The case records contained a description of the patient's pain distribution, and also a pain drawing which demonstrated clearly the distribution of symptoms. Also records of previous history of back pain or back pain surgery and size and position of the herniation. From this the presentation of the patients were classified into typical and atypical presentations.

Therefore a typical presentation was a patient, with no previous history of spinal surgery, with dominant leg pain with or without back pain and with or without neurological changes who had restricted straight leg raising and a disc herniation within the spinal canal or lateral recess. These numbered 515 patients (85%).

The atypical presentations numbered 90 patients

(15%) are as follows: (1) Dominant back pain with leg pain (34 patients). (2) Patients who had dominant leg pain due to a far lateral or foraminal herniation (14 patients). None of these required subsequent surgery. (3) Patients who had symptoms due to a recurrent herniation following previous discectomy (11 patients). All of these patients had relief of leg pain. (4) patients who had minimal leg pain but who had severe neurological symptoms such as a complete drop foot, marked weakness of foot plantar flexion or quadriceps weakness usually accompanied by paraesthesia or numbness in the same dermatome or dermatomes (3 patients). All of these patient had a rapid improvement immediately following chemonucleolysis and none of them had subsequent surgery. (5) Two level herniations in patients who had leg pain often with significant back pain, with herniations present at two adjacent lumbar levels. Often the symptoms would suggest one particular level, but in general both levels were injected. The majority of these patients who also had significant back pain prior to injection, ultimately had a two level fusion performed. (6) one patient had a cauda equina syndrome (Table 2).

All patients were managed routinely as described above apart from the patient with cauda equina syndrome. He presented with acute onset of bilateral anterior thigh pain, weakness of thigh muscles and numbness thighs and legs over two weeks. On admission, he was unable to stand unaided and bladder and bowel function were intact with numbness extending to the saddle area. He had a previous history of left sciatica for which he had an L4/5 and L5/S1 discectomy.

Table 2. Indications.

Indication	N (%)
Classical	515 (85%)
Non-Classical	90 (15%)
Leg pain with significant back pain	34 (6%)
Far lateral/foraminal herniation	14 (2%)
Recurrent disc herniation following surgery	3 (0.5%)
dominant neurology with minimal leg pain	3 (0.5%)
two level herniations	27 (4%)
Cauda equina syndrome	1 (0.1%)

my some years previously, and a recurrent right sided prolapse with a repeat discectomy leaving him with a right drop foot for which he used an orthosis. His MRI scan demonstrated a midline extra dural lesion at L2/3 thought most likely to be a disc herniation. A discography was performed with a non-ionic contrast (Omnipaque 240 mgm/ml) by slow injection of 0.5cc demonstrated the dye entering the herniation. The patient was sedated and one cc of Chymodiactin (2000 I U) was slowly injected over two minutes and was monitored closely for any neurological changes. He was subsequently able to stand unaided after 5 days, and at 3 months had fully recovered and returned to his non manual work. His pain score changed from 7.5 to 3.5 and his ODI from 80 to 38.

The average age of the patients was 47 years of age (range 17 – 88 years). Fifty six percent were male and 44 % female. The average duration of symptoms was 10 months (range 1-120 months), with right sided leg pain in 51% and left in 49%. During this period of time the availability of radiological investigation changed so that it was a myelogram in 42 patients, a CT scan in 206 and an MRI scan in 357 patients. We feel that the choice of investigation made little or no difference to the diagnosis as the primary reason for considering intervention was the patients symptoms (Table 3).

The majority of levels treated were single level at L5/S1 (296) and L4/L5 (264) with a small number at L3/4 (16) and L2/3 (2). Twenty seven double levels were treated where there were two level herniations with at least one on the same side with the possibility that one or other or both of these levels were the cause of symptoms. Also typically these patients had a greater tendency to have a greater degree of low back pain in relation to leg pain, and were advised

Table 3. Patient Demographics (605 cases, 1991-2000).

Mean Age	47 years (range 17-88)
Sex	M 56% W 44%
Duration of Symptoms	10 months (range 1 - 120)
Radicular pain	Right (51%); left (49%)
Investigation	Myelogram 42 patients; CT Scan 206 patients; MRI 357 patients

that they were at a greater risk of failure (Table 4).

The average follow up was 62 months, ranging from 12 to 123 months (Table 5). Seventy six percent of patients had good or excellent Macnab scores including those who had subsequent surgery and this equated well with 78 percent of patients who were satisfied with their result. The SF36 scores were compared by age and sex to the normal values for the local population. The relative study numbers were small, and in general equated closely to the normal local values. Eighty four patients (14 %) had subsequent surgery. Twenty four patients (4%) had fusion for persistent disabling chronic low back pain persisting for more than six months following chemonucleolysis. . The majority were two level cases and some patients who presented with dominant back pain before injection and were therefore not ideal candidates for chemonucleolysis. Fifty four patients (9%) had a decompression for persistent leg pain demonstrated by imaging to be due to persistent herniation. It is the author's experience that those patients tended to have a long history of leg pain, or had large herniations as shown in a previously previously randomised study conducted in the unit.^{52,53} None of these patients were from the recurrence following surgery and foraminal or far lateral herniation groups. Six patients (1%) had a further disc herniation at the adjacent or other level than the primary one treated by chemonucleolysis.

Complications

There were no complications related to the procedure (Table 6). Eight patients had readmission to hospital, three of these for suspected deep venous thrombosis following surgery, and the rest for persisting back pain following two level chemonucleolysis who ultimately went on to have an instrumented

Table 4. Distribution of injections.

L5-S1	296
L4-5	263
L3-4	16
L2-3	3
L4-5 & L5-S1	25
L3-4 & L4-5	2

fusion. There were no cases of infection, no neurological complications no cases of anaphylaxis, and no recurrent herniations at the same level. Six patients had a second herniation at another level, all treated by chemonucleolysis (Table 3); one patient had a fall in blood pressure which was corrected by infusion of one and a half litres of normal saline and without additional medication. He recovered normally thereafter. Because of the potential risk of sensitisation, these patients were premedicated with Chlorpheniramine maleate 6 mgs every six hours for 24 hours prior to the procedure to protect against possible anaphylaxis, accepting that this might alleviate the severity of anaphylaxis, but not prevent it.

Prior to this series, the author had trialled a series of over 300 patients who were RAST tested for allergy to chymopapain, prior to chemonucleolysis. Two suffered mild skin rashes (one RAST negative and one showing mild positive reaction) One patient had an anaphylactic reaction, the only one of over 2,000 procedures, and she was RAST negative. The use of the RAST test was discontinued. It is essential that all patients have a large bore IV inserted prior to the procedure to allow for rapid infusion on the rare occasion it may be necessary. In over 2,000 cases there was one case of discitis following injection. Two patients had a reduced blood pressure corrected by IV fluids; one had mild facial swelling and two mild skin

rashes occurred, in total 7 complications attributable to chemonucleolysis.

Discussion

This paper describes a consecutive series of patients presenting to a single spinal unit treated by chemonucleolysis who would equally have been considered suitable for surgical discectomy. At least one half of them were treated as a day case once it was realised that it was a suitable option. Seventy eight percent of patients were satisfied with their outcome which compares exactly with satisfaction outcomes for discectomy at 2 years in data from the Swedish Spine Registry.⁵⁵ The registry does not report the incidence of recurrent herniations, but shows that 12 per cent of patients who have a discectomy had previous spinal surgery.⁵⁵ No patients in this series had a recurrent herniation at the same level and this is significant considering that the recurrence rate at the same level following discectomy varies from 5 to over 27% within two years with an average of 5 and 10% at one and ten years.^{56,57,58} Aggressive discectomy reduces the risk but increases the longterm incidence of back and leg pain.^{59,60} Annular closure devices have been developed in an attempt to reduce the herniation level but the results are not conclusive.⁶¹ Nine per cent of patients did have surgery for continuing leg pain that had failed to subside within a reasonable time usually around 3 months and 91% of patients therefore did not require decompression surgery for their disc herniation. A feature of surgery at the same level following failed chemonucleolysis is that there is no fibrosis whatsoever in contrast to surgery for recurrent herniation where fibrosis and scar results in increased complications. Attempts to reduce the fibrosis have been tried but results are inconclusive.^{62,63} It has been previously shown that disc herniations occur at all ages and the degree of degenerative change in this group of patients is unrelated to age.⁵⁴ Also failures of chemonucleolysis occur most often in younger patients.⁵³ The pathology and presentation of acute disc herniation, as described in the materials and method, is quite different from that of spinal stenosis which is a chronic degenerative process, or spondylolisthesis. Four percent of patients in this series did go on to a spinal fusion due to persistent back pain following the chemonucleolysis

Table 5. Results.

Average Follow-up	62 months (range 12 - 123)
Macnab (Excellent and Good)	76%
Satisfaction	78%
Surgical Intervention	14%
Fusion/Stabilisation	4% (24 patients)
Decompression	9% (54 patients)
Chemonucleolysis	1% (6 patients)

SF-36 scores generally correlated with age/sex of normal scores for the local population.

Table 6. Complications.

Infection	0
Neurological	0
Anaphylaxis	0
Recurrent herniation	0

procedure. These patients were all either two level cases or had dominant back pain prior to chemonucleolysis and were therefore not ideal candidates. Publications of treatments for disc herniation do not report the subsequent numbers of patients who afterwards require a spinal fusion. However, the Swedish Spine Registry reports that 35 percent of patients who have a spinal fusion have had previous spinal surgery.⁵⁵ It is likely that many of these had a previous discectomy. The outcome of decompression surgery for lumbar herniated disc is influenced by the level of concomitant preoperative low back pain⁶⁴ and similarly the author has documented similarly that a poorer outcome is to be expected in patients with significant low back pain prior to chemonucleolysis.

There were no significant complications due to the procedure in this series of 605 patients; no infections, no neurological complications and no anaphylaxis although in over 2000 cases treated in the unit, there were two notable complications, one of anaphylaxis and one of infection. The other minor reactions, such as a drop in blood pressure, could have been due to medications or factors other than the chymopapain. Nordby et al reported that during the period 1982 – 1991, there were 121 adverse events reported to the FDA out of 135,000 patients, that is a complication rate of 0.09%.⁶⁵ He compared those to the largest series of surgical complications published by Ramirez and Thisted where the overall complication rate was 1.13%.⁶⁶ On these figures surgery has over twelve times the complication rate of chemonucleolysis. Dural tear is a complication of discectomy by whatever means, standard open, micro MIS endoscopic and endoscopic foraminal.⁶⁷⁻⁷¹ It usually does not have long term sequelae but the rare occurrence of CSF leak and iatrogenic meningoceal causes significant morbidity.⁷²⁻⁷⁵ Teli et al compares MIS endoscopic treatment with micro, and standard surgery and found increased dural tears in endoscopic discectomy.⁷⁶ In addition, Minimally Invasive Surgery does not decrease muscle damage as claimed compared to conventional surgery.⁷⁷ Chymopapain is injected usually using an 18 gauge (1.27 mm) needle. Ozone treatment is the only other minimal intervention treatment available with a similarly low complication rate to chemonucleolysis, but has had less usage and no long term follow up beyond two years.⁷⁸ Finally in the

USA, authors have shown significantly reduced costs comparing chemonucleolysis to surgery, taking all factors into account including further surgery.⁷⁹

This paper demonstrates that chemonucleolysis is a day-case procedure requiring a short operative time compared to surgery, which generally also requires an overnight stay. Nine percent of patients require surgery in the form of a decompression which compares favourably to surgery where 5 to 21 % may require a second surgery for a recurrent herniation.

Conclusion

Chemonucleolysis therefore is the most cost effective, least invasive and safest treatment available for soft disc herniation with an equal efficacy to other treatments; and has a large body of literature to support this. We owe it to our patients to make it available as a treatment.

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