

Therapeutics

A NEW APPROACH TO THE TREATMENT OF CHRONIC LOW BACK PAIN

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Summary 81 patients with chronic low back pain (average duration 10 years) were randomised to two treatment groups. 40 received an empirically devised regimen of forceful spinal manipulation and injections of a dextrose-glycerine-phenol ("proliferant") solution into soft-tissue structures, as part of a programme to decrease pain and disability. The other 41 patients received parallel treatment in which the main differences were less extensive initial local anaesthesia and manipulation, and substitution of saline for proliferant. Neither patients nor assessors knew which treatment had been given. When assessed by disability scores the experimental group had greater improvement than the control group at one ($p < 0.001$), three ($p < 0.004$), and six ($p < 0.001$) months from the end of treatment; at six months an improvement of more than 50% was recorded in 35 of the experimental group versus 16 of the control group and the numbers free from disability were 15 and 4, respectively ($p < 0.003$). Visual analogue pain scores and pain diagrams likewise showed significant advantages for the experimental regimen.

INTRODUCTION

OVER thirty years ago, one of us (M. J. O.) tried the effect of repeated epidural injections of local anaesthetic agents in patients with low back pain, on the supposition that most such pain was secondary to irritation of the dura or nerve roots. This treatment was rarely successful. Other pain-sensitive soft-tissue structures were then systematically evaluated by local anaesthesia, and it emerged that the ligaments and soft tissues of the low back were of primary import. At about the same time, Hackett¹ was injecting ligaments with various chemical agents in the hope of causing fibroblast hyperplasia and thus increasing their strength. When he claimed a cure rate of 82% in 1600 patients with low back pain other physicians took up the treatment,^{2,3-5} but progress in this area was retarded by reports of 3 cases of paralysis and 2 deaths after inadvertent injection of material (psyllium seed oil and zinc sulphate) into the subarachnoid space.⁶⁻⁸ On the theory that all sclerosants work in the same way, by causing an inflammatory response and thus fibroblast proliferation leading to new collagen production, M. J. O. chose to use dextrose-glycerine-phenol solution, originally developed for treatment of varicose veins; it has a good safety record and causes little pain. A treatment system was developed empirically, the main components of which were injection of dilute lignocaine to interrupt the pain reflex arc, a single forceful manipulation to ensure full range of movement, injection of "proliferant" solution into specific fascial and ligamentous sites, "disinflammation" of any accompanying

gluteal irritation with a single injection of corticosteroid, and repeated flexion exercises.

We have assessed this regimen in a double-blind trial. Because of the complexity of the regimen we departed from the traditional double-blind protocol in which only a single variable is studied. Instead we tested the entire system against a control system modified to include some but not all features of the full treatment programme.

PATIENTS AND METHODS

Patient Selection

Solicitations were mailed to 10 000 previously registered patients of the Sansum Medical Clinic (a multispecialty group), selected randomly and without regard to previous complaints of back pain. This was a computer-generated list based on zip codes. Patients were informed of the nature of the study and were invited to apply to participate if they had back pain of more than one year in duration that had not responded to previous conservative (non-surgical) treatment. 228 applications were returned. Patients were not interviewed if they were less than 21 or more than 70 years old, if they were pregnant or contemplating pregnancy, if they had litigation pending, if they had an unsettled worker's compensation claim, or if they were on disability pay. Other reasons for rejection before interview were body weight more than 25% over ideal (making injections technically more difficult), insulin-dependent diabetes, coronary artery disease, and debilitating medical conditions. Patients were arbitrarily excluded if they had fewer than 4 positive responses on the disability pain questionnaire (see assessment of outcome).

After the above exclusions a total of 117 patients were interviewed and examined by the three treating physicians (R. G. K., T. A. D., B. C. E.), 82 being accepted and 35 rejected. The reasons for rejection were recent exacerbation of chronic pain (3), overt psychopathology (3), radiographic osteoporosis (1), alcohol abuse (2), cervical myelopathy (1), upper rather than lower back pain (3), uncontrolled diabetes, angina or hypertension (4), aseptic necrosis or osteoarthritis of the hips (2), "total body" pain (2), unresolved litigation (2), other conservative treatment not tried (1), and refusal to participate (11). All patients accepted for the study had full clinical evaluations as well as lumbar spine and pelvic X-rays and laboratory tests to rule out infectious, neoplastic, metabolic, or inflammatory causes of back pain.

The patients had tried a wide range of non-surgical treatments, from chiropractic manipulation to acupuncture and corticosteroid facet injections. At entry into the study 49 (60%) were taking non-steroidal anti-inflammatory drugs and 6 (7%) were taking narcotic analgesics. The most common historical features were a need to change positions after prolonged posture (91%), avoidance of lifting heavy weights (70%), difficulty in getting out of a chair (65%), and pain interfering with sleep (65%). Only 17% had to restrict their walking to 30 min or less and 21% had to decrease their frequency of sexual activity. 9% of patients stayed at home most of the time because of their back pain and 4% stayed in bed most of the time. Patients were examined neurologically to rule out central and peripheral nervous system disease including acute radiculopathy. In all patients straight leg raising was possible to at least 70 degrees without pain.

Consent

All eligible patients were informed as to the nature of the study and the possibilities of side-effects or complications, including the remote possibility of death or paralysis. The study was approved and monitored by the Sansum Medical Research Foundation Institutional Review Board. Written informed consent was obtained from all patients.

Randomisation

Patients were allocated by the statistician (L. J. H.) into the experimental or placebo group by means of a random numbers

table. Patients were also randomly assigned to one of the three treating physicians for the double-blind treatment and to a different physician for the manipulation, which of necessity was single blinded.

Statistical Power

To have a power value of 90%, a total of 34 patients would be needed in each group, according to our estimates of an 80% response rate in the experimental group and a 40% response rate in the placebo group. The determination of sample size was based on a simple binomial proportion test to give 90% power with an alpha level of 0.05. By recruiting 82 patients for the study we allowed sufficient margin for attrition.

Other Treatments

Patients were advised to stop all pain medications except paracetamol (acetaminophen) and to avoid all other ancillary forms of treatment for back pain during the course of the study.

Injected Solutions

The experimental solution consisted of dextrose 25% (694 mosmol/l), glycerine 25% (2720 mosmol/l), phenol 2.5% (266 mosmol/l), and pyrogen-free water to 100%. Because this solution may cause a temporary irritation it was diluted with an equal volume of 0.5% plain lignocaine hydrochloride ('Xylocaine') to make it comparable with the placebo injection in terms of initial provocation of post-injection pain. Patients in the placebo group received sterile 0.9% saline. Each patient received six injections of approximately 20 ml of the same solution weekly. The solutions were identical in appearance and were prepared by a pharmacist using sterile techniques. Phenol has a characteristic odour that might be detectable if a drop of solution was spilled. This potential source of bias was eliminated by addition of phenol to the skin preparation throughout the study.

Protocol

Differences between experimental and control protocols are outlined in table 1.

Day one.—The study coordinator informed each of the three injecting physicians whether to administer the experimental or placebo treatment to each patient assigned to him for this day only. All patients were given 10 mg diazepam intravenously for relaxation and amnesia before the start of treatment. Patients in the experimental group were injected with 0.5% lignocaine in the following manner. The spinous process of L5 was identified and the skin overlying this area was sterilised and anaesthetised. A rigid 7.6 cm or 8.9 cm (19-gauge) needle was used for all injections. All injections were made from this single insertion into (1) tip of the spinous process of L4 and L5 and associated supraspinous and interspinous ligaments; (2) attachment of the ligamentum flavum along the borders of L4 and L5 laminae; (3) apophyseal joint capsules at L4-5, L5-S1; (4) attachment of the iliolumbar ligaments at the transverse processes of L4 and L5; (5) attachment of the iliolumbar ligament and dorsolumbar fascia to the iliac crest; and (6) attachments of the short and long fibres of the posterior sacroiliac ligaments, and the sacral and iliac attachments of the interosseous sacroiliac ligaments. Hackett⁷ described a characteristic pattern of referred pain from the sacrospinous and sacrotuberous ligaments. When this pattern was encountered additional injections were made from a separate entry point into the sacrospinous and sacrotuberous ligament origins along the lateral sacral border. A maximum of 60 ml 0.5% lignocaine was used in the experimental group patients. The placebo patients were injected at the same entry site(s) with 0.5% lignocaine, but no more than 10 ml was used. Gluteal muscle irritation, which we have found to be a nearly universal phenomenon in chronic back pain patients, was treated in the experimental group by infiltration of 50 mg triamcinolone in 10 ml 0.5% lignocaine into the fascial origin primarily of the gluteus medius muscle. The placebo patients were injected with lignocaine alone. A forceful manipulation was then performed in the experimental group patients. This was a modified version of the

TABLE 1—SUMMARY OF TREATMENT PROTOCOL

| | Experimental | Placebo |
|-------------------------|---|--|
| Day one (single-blind) | 1. Infiltration of 60 ml 0.5% lignocaine into specific sites 2. Forceful manipulation 3. Infiltration of triamcinolone into gluteus medius origin | Less than 10 ml 0.5% lignocaine injected at same sites Non-forceful manipulation Infiltration of lignocaine into gluteus medius origin |
| Day two (double-blind) | 1. Injection of proliferant into specific ligamentous and fascial sites 2. Repeated therapeutic flexion exercises | Injection of sterile saline into same sites Same as experimental group |
| Week 2-6 (double-blind) | Continued exercises and weekly injections of proliferant | Continued exercises and weekly injections of saline |

"typical" sacroiliac lumbar roll.⁹ The manipulation required an assistant to immobilise the thorax, the thigh being used as a lever to achieve a rotary and flexion strain across the sacroiliac and low lumbar areas. Patients in the placebo group received a manipulation in which they were placed on their side and pressure was applied from behind to the torso and buttocks simultaneously. This manoeuvre "rolled" the patient without producing any torsion across the lumbar spine or sacroiliac joints. Patients were amnesic for the procedure owing to the diazepam and were not told that two different forms of manipulation were being used. In no instance did a placebo patient indicate awareness that anything other than a "true" manipulation had been performed.

Subsequent treatment.—All subsequent injections were given in double-blind fashion by a physician who had not performed the manipulation. Patients in the experimental group received the first of six weekly injections of 20 ml experimental solution into the same sites as described above for the lignocaine injection, 0.2-0.4 ml being used at each site. Patients in the placebo group were injected with 20 ml physiological saline into these same sites. These injections were repeated weekly for the succeeding five weeks by the same physician in a double-blind manner. About 85% of patients in both groups requested and were given premedication with intravenous diazepam, with or without pethidine, to lessen the discomfort of the weekly injections. Patients in both groups were instructed in a specific series of flexion exercises. These exercises were continued during the injection period and for at least six months afterwards. The primary exercise consisted of standing with feet together and flexing forward at least 150 times daily. The exercises were modified to an easier sitting version in those patients for whom standing flexion proved too painful or vigorous. Although there is a theoretical objection to flexion exercises (increased intradiscal pressure), we have not found them harmful in the context of the present treatment regimen. All patients were repeatedly urged to use their backs and to perform previously painful activities.

Monitoring for Toxicity

During the week after each injection patients completed a comprehensive questionnaire about subjective complaints. All patients had a complete blood count, sedimentation rate, urinalysis, chemistry panel, and thyroid function tests done before the beginning of the study and after the fourth in the series of six injections. Abnormal values were followed up with repeat tests.

Assessment of Outcome

The success of any treatment for low back pain must rest on the patient's subjective assessment of pain and disability.¹⁰

Disability and pain scores.—We used a previously validated disability questionnaire designed by Roland,¹¹ consisting of 24 questions. An additional 9 questions were added from Waddell's chronic disability index,¹² making a total of 33. The disability pain score was calculated by adding the number of positive responses out of 33. The emphasis of these questions was on loss of function in the

performance of everyday activities rather than on the level of pain. A visual analogue pain scale represented by a straight line scored from a low of 0 cm (no pain) to a high of 7.5 cm (severe pain) was marked by the patient at all visits. Disability and visual analogue pain scores were assessed at baseline and one, three, and six months from completion of treatment. Each patient completed a pain diagram, which was analysed for area of pain by counting the number of grids marked. The maximum number of 102 included all tissue below the mid lumbar spine as well as the lower extremities. An analysis was made to identify the number of patients in each group with pain radiation into the lower extremity below the knee.

Clinical Signs

The injecting physician was not involved in the evaluation. All clinical signs were determined by an independent "blinded" observer who had no other contact with the study patients. (1) A modification¹³ of Schober's technique was used to measure anterior spinal flexion. Three marks were made on the skin with the subject standing erect. The first was at the lumbosacral junction, then 5 cm below and 10 cm above this point. The patient bent forward and the new distance between the upper and lower marks was measured. (2) The examiner's thumbs were placed over the posterior superior iliac spines of the standing or seated patient. The patient bent forward as far as possible and an estimate was made as to whether the upward movement of the thumbs was symmetrical.⁹ (3) Patients were examined from behind while standing erect for symmetry of range of motion. If there was a pelvic tilt these tests were performed with the patient seated. (4) Gluteal irritation was said to be present if there was visible asymmetry of movement of the buttock on forward flexion of the lumbar spine and localised spasm or fasciculation coupled with localised tenderness of the fascial origin of the gluteal muscle group.

Breaking of Code and Data Analysis

During the planning of the study the decision was made to observe the patients and analyse their disability and visual analogue scores double-blind for a minimum of six months from completion of treatment, and longer if the groups diverged without reaching statistical significance. All analyses including the calculation of Pearson correlation coefficients for the subjective and clinical data were performed by SYSTAT implemented on an IBM PC/AT. Statistical tests were based upon simple independent and dependent tests for continuous variables, and in those instances in which a variable was dichotomised, the Yates corrected chi-square was used.

RESULTS

After randomisation 42 patients were in the placebo group and 40 in the experimental group. 1 patient in the placebo group dropped out, leaving 81 for evaluation during the six months of double-blind follow-up. The two groups were clinically similar at entry (table II).

Subjective Scores

One month after treatment both groups had improved in terms of disability and visual analogue pain scores, but the improvement was significantly greater in the experimental group at this time and at three and six months (table III). 35 of 40 patients in the experimental group had greater than 50% improvement in disability scores, compared with 16 of 41 in the control group; and the numbers with zero disability scores at six months were 15 and 4, respectively ($p < 0.003$).

The pain diagram grid score likewise showed changes favouring the experimental treatment (table III). At the onset of the study 12 patients in the experimental group and 12 in the placebo group had pain radiating into the distal part of one or both legs. At six months this had resolved completely in 10 and 2, respectively ($p < 0.01$).

TABLE II—COMPARABILITY OF PATIENTS AT BASELINE

| | Experimental (n = 40) | Placebo (n = 41) |
|---|-----------------------|---------------------|
| Mean age, SEM (range) | 45, 2.08 (23-70) | 43.3, 1.66 (23-70) |
| M/F | 18/22 | 20/21 |
| Years of pain: | | |
| mean, SEM (range) | 8.98, 1.03 (1-30) | 10.72, 1.38 (1-35) |
| X-ray findings: | | |
| Normal | 11 | 12 |
| Disc narrowing | 6 | 12 |
| Degen changes | 3 | 2 |
| Disc and degen changes | 20 | 15 |
| Disability score (33 maximum) mean, SEM (range) | 11.45, 0.83 (4-26) | 11.83, 0.91 (4-26) |
| Visual analogue pain score (7.5 maximum) mean, SEM (range) | 3.76, 0.19 (1.5-7.2) | 4.0, 0.18 (1.2-6.0) |
| Pain grid score (102 maximum) mean, SEM (range) | 10.1, 1.24 (1-38) | 10.27, 1.6 (2-33) |
| No of patients with radiation of pain into distal lower extremity | 12 | 12 |

Clinical signs

Independent evaluation of physical signs revealed no significant differences between the groups after treatment. We tested the Pearson correlation irrespective of treatment group between all subjective and "objective" data recorded in the study. Only two physical findings showed a correlation ($p < 0.05$) with the visual analogue pain score at six months—namely, the return of rotational symmetry ($r = 0.315$) and the absence of gluteal irritation ($r = 0.271$).

Side-effects and Laboratory Data

Patients in both groups complained of pain and stiffness for 12-24 h after each injection; this was never severe enough to necessitate bed rest or absence from work. 2 patients in the experimental group and 1 in the control group had an increase in menstrual flow and 2 in the experimental group had postmenopausal spotting four weeks after starting treatment. 1 patient in the placebo group withdrew after the day-two injections because of severe headache and cough; these had resolved at follow-up a week later. There were no significant differences in laboratory data from the two groups.

DISCUSSION

The sacroiliac joint has a small range of motion, and when the joint is at the limit of its range no great force is needed to damage its ligaments.¹⁴ Once the ligaments of the low back and pelvis become incompetent, instability results.

TABLE III—SUBJECTIVE SCORES*

| | Placebo | Experimental | p |
|-------------------------------|--------------|--------------|--------|
| <i>Disability</i> | | | |
| Entry | 11.82 (0.92) | 11.45 (0.83) | — |
| 1 mo | 8.37 (1.04) | 4.00 (0.61) | <0.001 |
| 3 mo | 8.49 (1.04) | 4.70 (0.73) | <0.004 |
| 6 mo | 8.29 (1.10) | 3.43 (0.72) | <0.001 |
| <i>Pain (visual analogue)</i> | | | |
| Entry | 3.99 (0.19) | 3.78 (0.19) | — |
| 1 mo | 3.06 (0.29) | 2.13 (0.22) | <0.01 |
| 3 mo | 2.93 (0.25) | 1.77 (0.22) | <0.001 |
| 6 mo | 3.08 (0.28) | 1.50 (0.21) | <0.001 |
| <i>Pain (grid)</i> | | | |
| Entry | 10.27 (1.6) | 10.1 (1.24) | — |
| 6 mo | 8.24 (1.20) | 3.6 (0.37) | <0.001 |

*Mean (SEM).

This permits excessive external moments to be transmitted to the three-joint complex of intervertebral disc and zygapophyseal joints,¹⁵ and torsional stresses to be placed on the lumbar vertebrae and sacrum. The former may lead to disc and zygapophyseal joint degeneration and the latter to a slight displacement of the sacrum from its normal anatomic position,¹⁴ placing traction on pain sensitive structures and producing local as well as referred pain.

The treatment programme tested here has multiple components. We offer the following speculations as to why it is effective. The dilute lignocaine serves to interrupt the pain reflex arc and facilitate the manipulation. Triamcinolone "disinflammes" the gluteal muscles, which are subjected to chronic mechanical strain owing to the incompetence of the lumbar and sacroiliac ligaments. The manipulation moves the sacroiliac joint through a full range of motion, rupturing any microadhesions which may form in response to connective tissue immobilisation,¹⁶ and corrects any minor sacral malalignment present. The transient benefits previously demonstrated with manipulation¹⁷ are usually not sustained unless the supporting ligaments are strengthened. The proliferant induces an inflammatory response which leads to fibroblastic hyperplasia and the growth of collagen.¹ The exercises encourage synthesis of the extracellular connective tissue matrix,¹⁶ increase ligament junction strength,¹⁸ and induce proliferating fibroblasts to line up in parallel to existing connective tissue.¹⁹

In designing the protocol for the study we were faced with the dilemma of testing each component of the system in order to isolate its relative contribution, or testing the system as a whole. The repeated needling is painful, and it is a tribute to the study participants and a commentary on the desperate plight of patients with chronic pain that only 1 patient dropped out. We were unable logistically to justify treating a larger number of patients. We therefore elected to compare the complete system of treatment with a parallel but placebo system. Future studies may be needed to analyse the relative import of each component of the overall procedure. We conclude that the experimental regimen is a safe and effective treatment for chronic low back pain that has not responded to other conservative forms of treatment.

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Occasional Survey

MACROPHAGES AND ATHEROGENESIS

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UNTIL recently, practically all teaching and most research into atherosclerosis was based upon the hypothesis that focal haemodynamic intimal injury led to endothelial denudation, with subsequent platelet adhesion and degeneration. The release of platelet-derived growth factor in turn caused the recruitment into the intima, and proliferation therein, of smooth-muscle cells. Accumulation of lipid, both within cells and extracellularly, the laying down of connective tissue fibres and matrix, and basal necrosis completed the development of the lesions—the result being advanced plaques. Inherent in this view, the response-to-injury hypothesis,¹ was the conviction that most if not all of the cells in the lesion, including the lipid-laden foam cells, were derived from smooth-muscle cells. Much laboratory investigation of the development of atherosclerosis has therefore been based on this injury/platelet/smooth-muscle-cell hypothesis. The occasional notes of dissent, such as the Benditts' monoclonal hypothesis,² were regarded by most as only temporary diversions. However, the failure to demonstrate denuding endothelial injuries in human arteries and the lack of direct evidence of platelet involvement³ remained an inconvenience.

MONOCYTES, MACROPHAGES, AND ATHEROSCLEROSIS

The ascendancy of the smooth-muscle cell in atherosclerosis research dated from the early 1960s, when atherosclerosis became the subject of study by electron microscopy.⁴ Earlier in the century many investigators believed that monocytes or macrophages had a major role in atherogenesis, both in experimental models and also in human disease.⁵⁻⁷ It is only in the past few years that the macrophage has once again been investigated by those interested in the pathogenesis of atherosclerosis.

Real doubts of the dominance of smooth-muscle cells began with a series of papers on experimental diet-induced atherosclerosis, illustrating that the development of focal lesions was accompanied by ultrastructural evidence of monocyte adhesion to endothelial cells and their apparent

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