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Case Report

PENTOCLO Structural Treatment for a Severe Radiculopathy Related to Tightening Lumbar Postoperative Fibrosis: 3 Cases Report

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Abstract

Background: Postoperative Fibrosis (POF), one of major causes of failed back surgery syndrome, results in severe chronic disability with no curative treatment. Significant clinical and experimental results in the treatment of radiation-induced fibrosis prompted us to speculate that POF might respond to an antifibrotic treatment. Combined Pentoxifylline-Tocopherol (PENTO) was previously useful, as an antifibrotic treatment in a case of severe lumbar POF. Is addition of clodronate, an antimacrophagic agent, able to speed the PENTO effect on the unbalanced healing process, as observed in our experience in radiation sequelae?

Case Reports: 3 fairly typical patients developed, several weeks after surgery, severe periradicular, epidural and paravertebral POF, leading to chronic and unsatisfactory use of opioids for repeated surgery, or delayed surgery for a large herniated disc, or large infection with hematoma. Daily oral pentoxifylline- tocopherol- clodronate combination (PENTOCLO) was administered for 3 years, followed by 1-year PENTO maintenance, when stopping analgesics. Baseline and dynamic pain (visual analog scale), analgesic use and disability were assessed every 6 months. Enhanced-contrast lumbar MRI was performed at baseline and every 18 months. Baseline and acute back pain with sciatica progressively decreased (mean one third every 6 months) and completely regressed, until the patients led quite a normal life in 3 years. Progressive regression of the MRI baseline fibrotic area was postpone correlated with the patient's clinical improvement.

Conclusion: Antifibrotic treatment using PENTOCLO combination alleviated various patients' symptoms, because its structural effect was able to crush their lumbar POF. Additional studies are necessary to measure all the outlines of the effect.

Keywords: Clodronate; Neuropathic pain; Pentoxifylline; Postoperative epidural fibrosis; Recurrent low back pain; Tocopherol

Introduction

Surgical sequelae are related to faulty healing followed by local fibrosis, in the so-called the operative volume, worsened if hemorrhage, infection, or large/repeat surgeries.

Failures of herniated lumbar disc surgery is characterized by a postoperative chronic pain named failed back surgery syndrome [1], entity including persistent disc herniation (recurrent, incomplete), spine disability (spine instability, spondylolisthesis, facet joint syndrome, canal stenosis), sarco-iliac joint pain, and Postoperative Fibrosis (POF) in 8-14% but its impact seems to be underestimated [2]. Epidural and periradicular POF, located near a lumbar root, can induce neural tension which increases during forced stretching or repeated movements, leading to permanent radiculopathy [3,4].

Today, there is no structural treatment to reduce POF. Symptomatic management includes salvage surgery with decompression/fusion procedure [5] and neuropathic pain treatments including anti-inflammatory drugs, analgesics (codeine, tramadol, morphinic), neuromodulators (gabapentin, antidepressants, benzodiazepines), epidural-intradural injections and spinal cord stimulation [6].

Based on pathophysiological knowledge, an antifibrotic treatment combining pentoxifylline-tocopherol and clodronate (PENTOCLO) has been successfully developed for patients

suffering from severe radiation-induced sequelae [7]: it helped to reach, for the first time, complete resolution of symptomatic postoperative fibrosis and its related chronic pain.

Cases Report

Three patients who underwent lumbar spine surgery, after immediate postoperative improvement developed, after several weeks, worsening permanent back pain and sciatica.

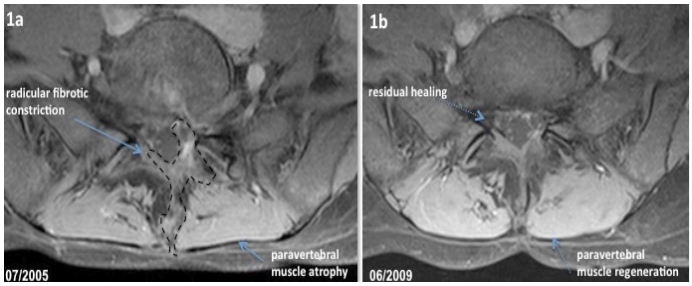
The pain was progressively intense, with a high and constant basal level all day and night long, whatever body position standing, sitting or laying, without rest help. This basal pain should related to the fibrotic process itself, referring to a permanent nerve "strangulation", in contrast of the acute pain, more related to scar stretchting or mechanic worsening during movement. Lumbar MRI confirmed various contrast-enhanced fibrosis, along operative course (unwell measurable volume), in relation with patient's symptom, without disc herniation. Pharmacologic management for pain has combined NSAID, gabapentin/ pregabalin, antidepressant, analgesics in a released form and paracetamol. However, pain was, step by step, uncontrolled, resistant despite opioids, scored above 5/10 using a Visual Analog Scale (VAS).

Because of our knowledge and reputation on fibrotic process, patients self-presented in our tertiary care facility (Hôpital Saint Louis) with these recalcitrant low back pain and sciatica, without motor nerve damage. Oral PENTOCLO combination was then started using 800 mg pentoxifylline- 1000 IU tocopherol daily and 1600 mg clodronate 5 days/week (from Monday to Friday), alternated with 20 mg piroxicam (2 days/week).

Drug safety was good, as known for several decades, with initial transient headache and nausea-epigastric pain in relation with pentoxifyllin. Analgesic agents were prolonged, but dosages were progressively reduced (every 3-6 months), then one by one stopped, whenever maximum pain slowed under 4-5/10. Physical therapy was stopped: risk of traction distracting lumbar fibrosis was too high, lassoing nerve root *via* the operative course stretching. Clinical assessment including VAS back pain and sciatica, analgesic drugs and mobility every 6 months, and lumbar MRI every 18 months.

- **Patient 1:** A 27-year-old woman underwent extraligamentar hemilaminectomy in 2004/09, after 9 months of resistant left S1 sciatica and beginning of foot paresthesia related to a down-luxated large herniated L5-S1 disc. After a 7 weeks of complete symptom resolution, she developed gradually worsening low back pain, then severe left sciatica. In 2005/07, lumbar Magnetic Resonance Imaging (MRI), ruled out disc herniation and showed a left S1 periradicular scar prolonged by a hacked fibrotic operative course (Figure 1a). Pain was resistant to analgesics, external stimulation and two epidural injections.

In 2005/11, she experienced permanent back and leg 6-7/10 basal pain and a daily unbroken 4-hour 9/10 acute phase, especially sitting. Clinical improvement began 3 months after PENTOCLO initiation. After 6 months, basal pain decreased to 3/10, with a 2-hour 8/10 acute phase of, and no MRI change. After 12 months, basal pain decreased to 1-2/10 and dynamic pain to 4/10, with a 1-hour 8/10 acute phase of twice a week: she walked again. After 18 months, total rest was possible lying down, lumbar pain was intermittent 1/10 during the day or 1 h of truncated 7/10 sciatica, while MRI showed a significant decrease in the area of fibrosis. At 24 months, she was much better (only occasional tramadol). At 30 months of PENTOCLO treatment, in 2008/05, basal pain was 1/10 (discomfort) and dynamic pain 4/10, while MRI showed minimal residual fibrosis. Maintenance therapy using combined pentoxifylline-tocopherol (PENTO) alone was begun for one year while the patient returned to work. At 42 months, occasional radicular pain appeared after sport, while any analgesic was stopped. The last MRI showed complete regression of the original fibrotic area (Figure 1b). Antifibrotic treatment PENTO was stopped in 2009/12, with no recurrence of pain 1 year after stopping drugs.

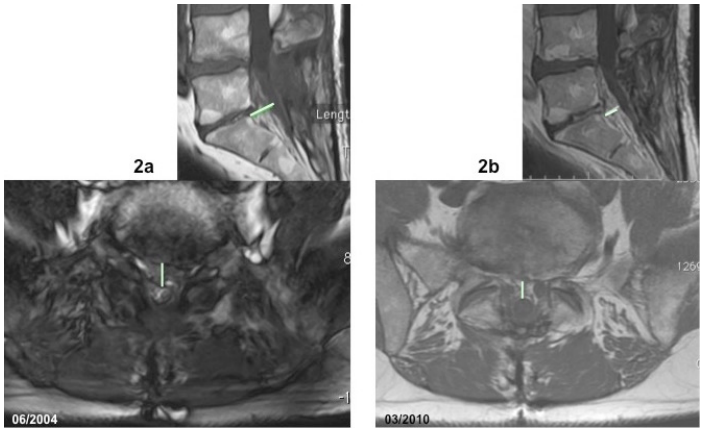


Figures 1(a,b): Patient 1: Laminectomy for large L5-S1 herniation- (a) postoperative sagittal and axial MRI with left S1 nerve root scar tissue (enhanced after gadolinium injection in T1 sequence) prolonged by hacked fibrotic operative course (arrow); (b) soft tissue fibrotic strong reduction combined with paravertebral muscle regeneration after 4y PENTOCLO treatment.

- **Patient 2:** A 25-year-old foreman underwent a successful right L4-L5 discectomy in 1978 for disc herniation, then a 2nd successful left L5-S1 discectomy in 1984. At 50 years old, after 8 years of progressive right foot paresthesia and motor weakness, he underwent spine surgery for a 3rd time: L4-L5 laminectomy (2003/08) reducing disc protrusion with canal stenosis (osteophytosis). This afforded pain relief but there was persistent right distal steppage gait,and left progressive radicular pain: MRI showed thick epidural fibrosis (2cm) obstructing the lumbar canal (infracentimetric, Figure 2a).

In 2004/04, the patient had an intolerable permanent 8/ 10 left sciatica, right foot paresthesia, and dysuria related to neurological bladder (cauda equina).

After PENTOCLO initiation and analgesic adjustment, improvement began during the first month. After 6 months, he described intermittent R foot paresthesia and cramps, daily 4/10 basal L pain: he resumed work and stopped NAIS, tramadol and paracetamol. After 12 months, left basal sciatica was foot truncated and reduced (2/10) and dynamic pain 4/10, while dysuria and frequent urination decreased from 10 to 4 times/day (stop gabapentin). After 18 months, MRI showed a significant (mean 1/3) decrease in fibrotic thickness. At 24 months, the patient experienced once a week R foot symptom, and L truncated 1-2/10 intermittent daily pain. At 30 months, no R pain except if sitting, while L basal discomfort remained. In 2007/11, at 42 months, PENTOCLO treatment was stopped with simple discomfort, no attack of pain or perineal symptoms, while MRI showed significant decrease (half) in the epidural fibrotic area allowing 1.5 versus 1 cm lumbar canal (Figure 2b). Maintenance therapy using combined PENTO was begun for 18 months (5 years of antifibrotic treatment). The patient retired in 2010/04. Stable residual 1-2/10 discomfort persisted in 2012/05 with occasional pain when traveling (probably mechanic), 2 years after stopping drugs.

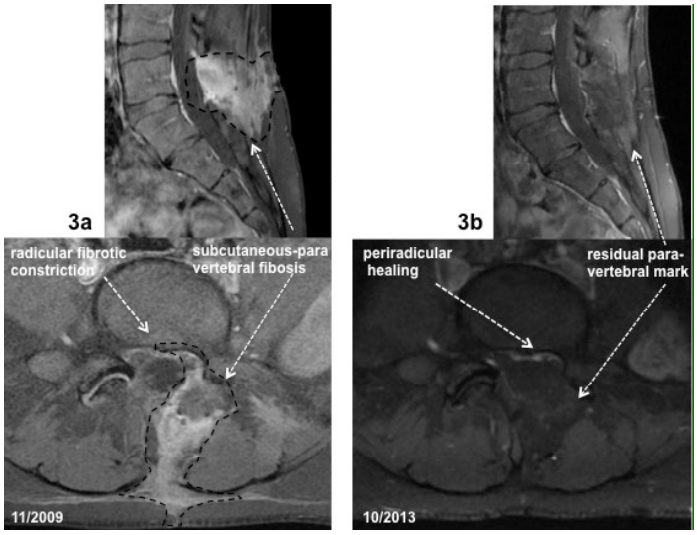


Figures 2(a,b): Patient 2: repeated L5-S1 surgery- (a) postoperative sagittal and axial MRI with extensive epidural fibrosis (line); (b) half thickness fibrosis reduction after 5.5y PENTOCLO treatment.

- **Patient 3:** A 25-year-old woman experienced left sciatica in 2009/02, then big toe paralysis, in relation to an L5-S1 disc herniation that required rapid spine surgery. She developed immediate lumbar and left sciatica related with a large lumbar scar infection. MRI revealed small disc protrusion and major periradicular and paravertebral fibrosis: 5 epidural injections were followed by a second L5-S1 discectomy (2009/08) with fibrotic dissection. After a modest transient postoperative improvement, she developed worsening permanent lumbar pain and sciatica, progressively resistant to analgesics. Sagittal MRI (2009/10) showed a 6x6 cm area of fibrosis with left paravertebral liquid mark and right root extension (Figure 3a).

In 2010/01, the patient self-presented in our hospital with 2 crutches for walking and uncontrolled pain under opioids: 7/10 basal back pain and left sciatica day and night, standing or laying, and a daily 4H acute phase (9/10 dynamic pain), combined with a right truncated sciatica (buttock).

Clinical improvement began 3 months after PENTOCLO initiation, while drug safety was good. After 6 months of PENTOCLO, pain was more acceptable (6/10 basal, 8/10 dynamic) and lumbar relief in bed allowed hours of sleeping. After 12 months, she experienced pain reduction (5/10 basal, 7/10 dynamic) using one crutch. At 18 months, she could walk again: R sciatica had resolved, while back pain and L sciatica reduction (4/10 basal, 7/10 dynamic); MRI indicated half reduction and less dense fibrotic volume. After 24 months, she was again "taking part in life" and planned to reduce opioids (by half): 3/10 basal pain with possible recovery in 1H, 6/10 dynamic. At 30 months, daily basal pain was 1/10 (discomfort), and dynamic pain 4/10. At 36 months, L sciatica was intermittent with an effort; MRI showed two third fibrotic regression. At 42 months (2013/07), she returned to work with occasional truncated L radicular pain after sport and stop opioids; MRI showed quite complete regression of the original periradicular and paravertebral fibrotic area (Figure 3b): PENTOCLO was stopped while a maintenance therapy using combined PENTO alone began. At 5 years, she had occasional residual pain with normal life (even dance!) and without any specific treatment.



Figures 3(a,b): Patient 3: Surgery for L5-S1 disc herniation followed by infection, then salvage surgery- (a) postoperative sagittal and axial MRI: radicular constriction with extensive left paravertebral fibrotic area (arrow) and right root extension (b) periradicular healing with residual paravertebral mark: quite complete fibrosis regression after 4y PENTOCLO treatment.

Discussion

These 3 patients with intolerable progressive lumbar POF, a mean 9 months after their last surgery, experienced a dramatic improvement thanks to an antifibrotic PENTOCLO treatment, with progressive "exponential-like" pain resolution, while MRI fibrotic regression was closely but postpone correlated with patient's clinical response.

Patients' pain was related to POF because of the pain-free interval (weeks) after surgery, the gradual onset, its neuropathic characteristics without recurrence of disc herniation or mechanic cause. The radicular pain mechanism due to fibrosis is debated: some POF seen on MRI is asymptomatic, while major pain and disability were associated with slight but tight POF [8]. To interpret the postoperative imaging correctly, it is necessary to understand the nature of the surgical complication, best interpreted by contrast-enhanced MRI [9]. There is, nevertheless, a definite correlation between extensive POF and postoperative symptom severity [10]. POF pathophysiology enhanced extensive or repeated surgical manipulation of tissue, bleeding, dural tears and irritation from mechanical instability [11]. Moreover, large initial herniated volume or prolonged herniation cause venous obstruction then vascular hypoxia, leading to "perineural fibrosis and neuronal atrophy" [11].

Horizontal and sagittal contrast-enhanced MRI was clearly a helpful tool for diagnosis, during initial consultation, helping to characterize touch and intensity of the patient's pain description. If radiculopathy is easily understood by the direct scar effect round the nerve root, it is also generated by an indirect strangulation, *via* a thick operative route creating a "lasso effect" when sitting (fibrotic stretching). Lumbar back pain is related to extended fibrosis involving paravertebral muscle, also worsened if movement (fibrotic stretching).

There are few literature reports of POF treatment, except for symptomatic treatments, while reintervention for scar tissue excision may be dangerous, and worsens symptoms in 20% of cases [2]. The pathophysiological understanding of the fibrotic process, characterized by non-specific changes in the vascular connective tissues involving excessive extracellular matrix deposition, fibroblast proliferation and the presence of an inflammatory infiltrate, led us to envisage a fibrotic reduction via the antioxidant pathway.

First, *in vitro*, *in vivo*, and clinical trials using PENTO combination was built in 90's for their properties and safely to reduce radiation-induced fibrosis [12,13]. If, drugs alone were unable to modify fibrosis, they possessed all biological properties to make them excellent antifibrotic agents. Pentoxifylline, used clinically for vascular diseases, had *in vivo* properties as anti-TNFα, erythrocyte flexibility, vasodilatation, anti-inflammatory reaction, and *in vitro* antioxidant properties, inhibition of fibroblast proliferation and matrix production. Tocopherol's scavenge ROS generated during oxidative stress, and protect cell membranes against lipid peroxidation.

Delanian et al. showed in a randomized clinical trial, that 6 months radiofibrotic regression was significantly better using PENTO (60%) versus double placebo (40%) $p<0.01$ [7], then confirmed in an experimental pig model allowing a histopathological tissue normalization [6]. After an exponential regression, PENTO optimal duration was longer than 12 months to avoid a rebound effect. The biological rationale of fibrogenic action was developed *in vitro*: pentoxifyllin and vitamin E act synergistically to inhibit TGF-β1 transcription [13].

One patient with concomitant breast radiofibrosis and lumbar fibrosis experienced a surprising clinical improvement in both [personal communication]. We first reported, in 2004, a case of severe painful POF in which we achieved progressive improvement with PENTO combination [14]. Moreover, Pentoxifylline successfully prevented compartment syndrome in rats in dorsal root ganglia caused by exposure to *nucleus pulposus* [15].

The PENTOCLO combination was built later (in 2002) using a synergical effect of PENTO and clodronate an old and safe bisphosphonate. PENTOCLO was able to reduce the delay of radiation fibrotic response, to heal mandible osteoradionecrosis (clodronate is able to inhibit macrophagic bone destruction) [16], and to improve symptoms in progressive radiation peripheral neuropathy (clodronate inhibit macrophagic myelin nerve destruction in rats) [17].

Pain resolution seems do not correlate timely with MRI fibrotic response. This critical time-lag response was previously observed after treatment of radiation breast fibrosis: first a clinical softening corresponding to changes in the fibrotic tissue texture, followed by a measurable volume regression [personal communication]. Histologically, the homogeneous fibrosis changed in a heterogeneous tissue as a patchwork, before a fibrotic volume reduction [7]. While no clear assessment of tissue changes elasticity is today available, contrast-enhanced MRI shows a "airing" fibrotic area (as impressionist painting), then measure a delayed volume reduction.

Conclusion

PENTOCLO treatment, that already improved cancer survivor's life by reducing various radiation sequelae, may be useful in medicine as a structural method of treating symptomatic postoperative fibrosis, because it contributes to a progressive and strong fibrotic volume reduction and related tightening: a clinical trial is in progress.

Conflict of Interest

None.

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