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Serum Beta-endorphin Changes in Lumbar Facet Syndrome Treated with Radiofrequency Lumbar Facet Denervation – A Randomized Controlled Study

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Abstract

Background: Lumbar facet joint has been considered a significant source of chronic low back pain (LBP). Radiofrequency (RF) lumbar facet denervation is an effective treatment modality for patients with lumbar facet syndrome (LFS). We propose this protocol to study the effect of RF and the change in serum beta-endorphin level in the treatment of LFS.

Methods: This open-label, parallel, randomized controlled clinical trial enrolled patients with LFS. The study subjects were randomly assigned equally into two arms. The treatment arm received percutaneous RF and the control arm received medical treatment using non-steroidal anti-inflammatory drugs (NSAIDs). Patients were evaluated at days 0, 7 and 28 after randomization. Primary endpoints were the pain visual analogue scale on day 28. Secondary endpoints were visual analogue scale on day 7, quality of life evaluation using short-form 36 (SF-36) questionnaires and serum beta-endorphin level on days 0, 7 and 28.

Results: Until August of 2008, twenty-five patients were enrolled, including eleven in the treatment arm and fourteen in the control arm. Baseline characteristics between these two arms were comparable regarding age, sex, pain intensity, serum beta-endorphin level and short-form 36 score. The mean postoperative 7-day visual analogue pain scale for patients who had LBP in the control and treatment arm was 6.5 and 3.0. The mean postoperative 28-day visual analogue pain scale for patients who had LBP in the control and treatment arms was 6.0 and 2.5. On average, patients in the treatment arm had reduction of serum beta-endorphin compared to the control arm on day 7 (38.5% vs 0, p=0.141) and day 28 (37.9% vs 0, p=0.621).

Conclusion: RF lumbar facet denervation is an effective treatment modality and better than NSAIDs for patients with LFS. RF lumbar facet denervation demonstrated a trend to reduce serum beta-endorphin levels, although not statistically significant.

Keywords: Lumbar facet syndrome; Radiofrequency; Facet denervation; Beta-endorphin

Introduction

Chronic low back pain (LBP) is an important health issue as approximately 80% of adults will experience at least one episode of LBP during their lifetime. Facet joints have been implicated as a cause of chronic pain in 15% to 40% of patients with chronic LBP [1,2].

The facet joints are true synovial joints, innervated by the medial branches of the dorsal rami from the spinal nerves.

Lumbar facet syndrome (LFS) was first described by Ghormley in 1933 [3]. Theoretically, facet joint pain can be treated by denervation of the medial branches of the dorsal rami, which supply the sensory innervation to the joints [4-6]. After a detailed anatomical study of the lumbar zygapophysial nerve supply by Bogduk and Long in 1979 [2], several studies had shown initial pain relief using radiofrequency (RF) medial branch neurotomy [7,8]. Two main mechanisms contributing to the relief of pain using this approach include the release of endorphins and a local anesthetic effect [9]. However, there has been no direct comparison between RF denervation and non-steroidal anti-inflammatory drugs (NSAIDs).

This study was an open-label, parallel, randomized, controlled clinical trial to investigate the efficacy, safety, and possible mechanisms involved in the use of RF denervation in the treatment of LFS.

Materials and Methods

Study design

This was an open-label, parallel, randomized, controlled clinical trial. The study was approved by the Institutional Review Board of

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our hospital. Written informed consent was obtained from all subjects before enrollment.

Patients selection

Ninety-six adult patients with LFS were initially screened for this study. The inclusion criteria were: (1) continuous LBP (with or without radiating pain into the upper leg) for more than 6 months with focal tenderness over the facet joints; (2) no radicular syndrome should be present (i.e., no sensory or motor deficits and no positive straight leg raise test); (3) no evidence of any disc bulging (without apparent nerve root compromise) was found on the CT or MRI studies; (4) no radiological evidence of instability was noted on dynamic spinal imaging; (5) three or more clinical features including: pain during prolonged standing, pain during prolonged sitting, pain during prolonged bed rest, pain deteriorated during hyperextension rather than hyperflexion, pain improvement after repeated motion); (6) a minimum age of 20 years [10]. Patients were excluded from the study of they had any of the following: prior radiofrequency treatment, coagulation disturbances, allergies for radiopaque contrast or local anesthetics, malignancy, pacemaker insertion or other implanted electronic device, active infection, mental handicap or psychiatric condition precluding adequate communication, language problems, or pregnancy,

Randomization

The study patients were randomized (in a 1:1 ratio by computer-generated allocation) to receive either RF denervation or NSAID treatment. A research nurse, who was not involved in assessing patient outcome, performed the randomization via pre-sealed envelopes. All subjects were treated by a neurosurgeon who was not involved in the randomization allocation.

Interventions

The study subjects were randomly assigned to either treatment (RF denervation) or control (NSAID) groups. The treatment group received bilateral percutaneous RF from L3 to S1. The patient was placed in the prone position on the operating table. The anatomical landmarks for the spinal structures reflected on the skin were marked under fluoroscopic guidance. The skin was sterilized in standard fashion. Local anesthesia with 2% lidocaine was injected into the subcutaneous tissue but not extended. A 10-cm, 22-gauge curved tip cannula with a 10-mm exposed tip was introduced into the medial branch of the distal portion of the spinal posterior rami nerve under fluoroscopic guidance. An RF generator (Baylis® medical company, 5959 Trans-Canada Highway Montreal, QC H4T 1A1; product number: PMG-115) was used for all RF denervation procedures. Stimulation at 5 Hz, with 0.5 m sec pulse duration, was used to confirm the nerve position. The RF lesion was created by passing the electrode through the nerve to raise the tissue temperature to 80 °C for 90 seconds. The inducer cannulas were removed and the wound was covered with gauze. The control group received medical treatment using NSAIDs, as prescribed by their physician.

Endpoints

Patients were evaluated at baseline and days 7 and 28 after intervention. The primary endpoint was a difference in VAS pain score over the lower back and hips between the two groups on day 28. Secondary endpoints were VAS on day 7, quality of life evaluation using short-form 36 (SF-36) questionnaires, and serum beta-endorphin levels on days 0, 7 and 28. Serum levels of beta-endorphin were measured using commercial kits.

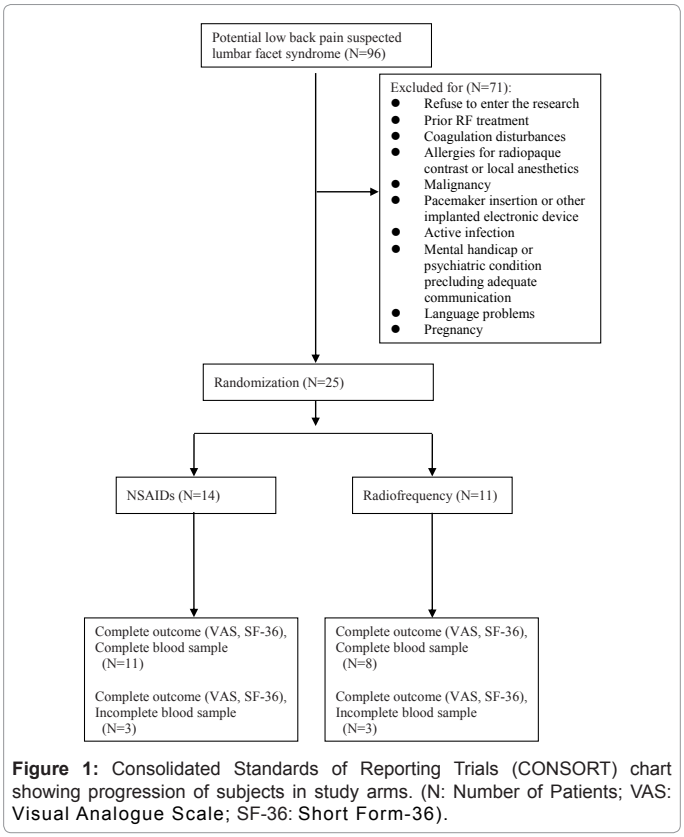

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) chart showing progression of subjects in study arms. (N: Number of Patients; VAS: Visual Analogue Scale; SF-36: Short Form-36).

Statistical Analysis

This is an open pilot study to explore the difference between radiofrequency and NSAIDs. Hence, we did not have previous data to perform sample size calculation and power analysis. The Student's t-test was used to compare differences between the two groups including demographics, VAS, SF-36, and serum beta-endorphin levels. The Statistical Package for Social Sciences version 19.0 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. Significance was set at a p-value < 0.05.

Results

The Consolidation Standard of Reporting Trials (CONSORT) chart is shown in Figure 1. Ninety-six adult patients were screened and 25 patients were randomized, including 11 to the treatment (RF) group and 14 to the control (NSAID) group. There were six male and eight female patients in the control group with a mean age of 55.4 ± 10.0 years. There were five male and six female patients in the treatment group with a mean age of 55.8± 12.4 years. The median baseline low back/ loin/ hip pain VAS of patients in control vs. treatment groups was 7.0 vs. 5.0, respectively (p>0.05). Baseline demographic characteristics and clinical symptoms were comparable between the two groups (Table 1).

The clinical outcome measurements are listed in Table 2. Significant reduction in VAS pain scale over the lower back, loin, and hip were found in the RF group, compared with the NSAIDs group on day 7 (6.5 vs. 3.0, p<0.05) and day 28 (6.0 vs. 2.5, p<0.05). There was no significant difference between control and treatment groups regarding quality of life as reported by short-form 36 (Table 2). No significant adverse events were found in this 28-day study.

As shown in Figure 1, three patients from each treatment arm were excluded due to incomplete blood samples. Finally, 11 patients

	NSAID	Radiofrequency	
	(n =14)	(n =11)	p-value
Demography [a]			
Age	55.4 ± 10.0	55.8 ± 12.4	0.928
Gender (Female %)	8 (57.1)	6 (54.6)	1
Systolic pressure	135.9 ± 19.1	125.8 ± 14.1	0.174
Diastolic pressure	76.1 ± 8.9	74.6 ± 12.0	0.738
Visual analogue scale [b,*]			
Shank pain	5.0 (1.0, 6.0)	2.0 (0.2, 7.0)	0.524
Thigh pain	0.0 (0.0, 1.0)	0.0 (0.0, 6.0)	0.258
Low back, Loin, Hip pain	7.0 (5.0, 8.0)	5.0 (3.0, 7.0)	0.094
Foot anaesthesia	0.5 (0.0, 2.0)	1.0 (0.0, 7.0)	0.519
SF-36 [b,#]			
Physical Functioning	65.0 (50.0, 70.0)	65.0 (45.0, 80.0)	1
Role Physical	25.0 (0.0, 75.0)	0.0 (0.0, 0.0)	0.013
Bodily Pain	52.0 (42.0, 64.0)	53.0 (42.0, 80.0)	0.645
General Health	57.0 (52.0, 57.0)	60.0 (52.0, 67.0)	0.388
Vitality	55.0 (50.0, 55.0)	50.0 (50.0, 65.0)	0.861
Social Functioning	50.0 (37.5, 50.0)	38.0 (25.0, 50.0)	0.111
Role Emotional	67.0 (66.7, 100.0)	33.0 (0.0, 66.7)	0.067
Mental Health	56.0 (48.0, 60.0)	60.0 (44.0, 60.0)	1

[a] mean ± SD; [b] median (Q1, Q3)
*The higher the score, the worse the outcome
#The higher the score, the better the outcome

Table 1: Baseline demographic characteristics and clinical characteristics of lumbar facet joint syndrome patients.

	Day 7		Day 28	
	Control	Surgery	Control	Surgery
	(n=14)	(n=11)	(n=14)	(n=11)
VAS [a]				
Shank pain	1.0 (0.0, 4.0)	1.0 (0.2, 4.0)	2.5 (0.0, 4.0)	2.5 (0.1, 3.0)
Thigh pain	0.5 (0.0, 2.0)	0.3 (0.0, 3.5)	1.5 (0.0, 5.0)	2.0 (0.2, 3.5)
Low back, Loin, Hip pain	6.5 (5.0, 8.0)	3.0 (1.8, 5.0)*	6.0 (5.0, 9.0)	2.5 (2.0, 4.5)*
Foot anaesthesia	1.0 (0.0, 4.0)	0.2 (0.0, 6.0)	1.3 (0.5, 5.0)	3.0 (1.0, 4.0)
SF-36 [a]				
Physical Functioning	-	-	60.0 (45.0, 70.0)	65.0 (45.0, 80.0)
Role Physical	-	-	25.0 (0.0, 75.0)	25.0 (0.0, 75.0)
Bodily Pain	-	-	42.0 (41.0, 64.0)	31.0 (31.0, 74.0)
General Health	-	-	55.0 (52.0, 60.0)	62.0 (47.0, 65.0)
Vitality	-	-	55.0 (50.0, 60.0)	55.0 (40.0, 60.0)
Social Functioning	-	-	37.5 (37.5, 50.0)	37.5 (37.5, 50.0)
Role Emotional	-	-	33.3 (0.0, 66.7)	66.7 (0.0, 100.0)
Mental Health	-	-	60.0 (56.0, 64.0)	56.0 (36.0, 56.0)*

[a]median (Q1, Q3)
*p-value < 0.05

Table 2: Comparison of clinical characteristics through day 7 and day 28.

comprised the control (NSAIDs) group and eight patients comprised the treatment (RF denervation) group.

Serum beta-endorphin levels are shown in Figure 2. At baseline, patients in the treatment group had higher serum beta-endorphin levels compared with the control group (2.15 ± 0.06 vs. 0.02 ± 0.01 ng/dl, respectively). There was a trend towards reduction in serum beta-endorphin levels in the RF group, compared with the NSAID group on day 7 (38.50% vs. 0, p=0.141) and day 28 (37.88% vs. 0, p=0.621), although the differences did not reach significance.

Discussion

This is the first open-label, parallel, randomized, controlled study comparing RF denervation with NSAIDs based on clinical endpoints and serum beta-endorphin levels. We demonstrated that RF lumbar facet denervation benefited patients with LFS. However, there was no significant difference in serum beta-endorphin levels between RF denervation and NSAID groups.

Compared to the NSAID group, our patients with LFS who received RF denervation tended to have better pain scale outcomes until day 28. Past studies have reported that RF did not produce permanent pain relief because the nerve eventually regenerates, usually within 12-18 months [11]. Lord et al. found the median time for return to 50% of pre-procedural pain was 263 days [12]. Dreyfuss et al. found that pain relief may last for approximately 12 months. Thus, repeat treatment may be necessary in some patients.

The mechanism underlying the relief of pain after RF treatment is still unclear. In animal studies, pulsed RF to a dorsal root ganglion has been shown to induce c-fos expression in laminae I and II of the dorsal horn at both 3-hours [13] and 7-days [14]. However, continuous RF treatment did not have this effect. Previous articles have reported that c-fos gene expression leads to the formation of a second RNA messenger, preprodinorphin, which in turn increases the endorphin production to modulate the analgesic action [15]. Expression of this gene also appears to act on the inhibitory and excitatory neurons within the dorsal horn of the medulla [16].

To date, no data on beta-endorphin change after RF denervation has been reported. Endogenous opioid peptide release is a possible mechanism underlying the analgesic effect of electrical acupuncture (EA) and transcutaneous electrical nerve stimulation (TENS) [9]. The antinociceptive effects induced by EA and TENS were compared in rats [17]. Wang et al. found no significant difference in the production of antinociception for two different peripheral conditioning stimuli when applied to the same sites. They felt that common neural mechanisms were most likely involved in processing the analgesic effects of EA and TENS [17].

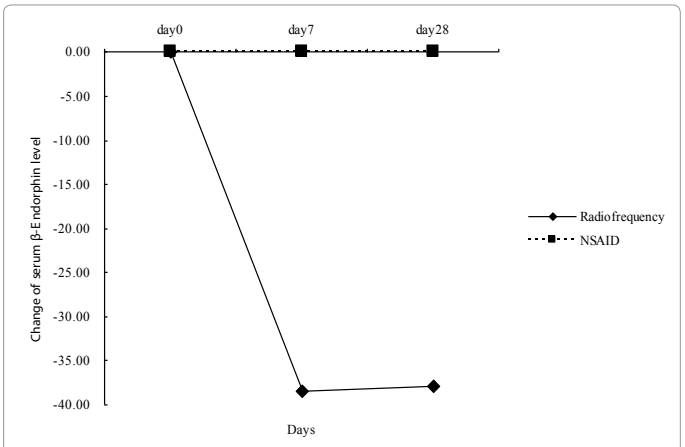

Figure 2: Mean change from baseline to day 7, 28 in β-Endorphin level (ng/ml) (N=19), *p-value <0.05, data value is the median (Q1, Q3). The 7th day, Surgery group -38.50 (-88.23, 0.36)%; Control group 0.00 (-13.33, 118.18)%, p=0.141. The 28th day, Surgery group -37.88 (-91.29, 160.04)%; Control group 0.00 (-20.00, 27.27)%, p=0.621.

High and low frequency stimulation induced by EA has been shown to release different types of endorphins [18]. Elevated resting plasma beta-endorphin may be a potential biomarker for reduced endogenous opioid analgesic capacity in patients with chronic pain. Further studies have shown that different kinds of neuropeptides are released by EA at different frequencies. For example, EA of 2 Hz accelerates the release of enkephalin, beta-endorphin, and endomorphin, while an EA of 100 Hz selectively increases the release of dynorphin. A combination of the two frequencies produces a simultaneous release of all four opioid peptides, resulting in maximum therapeutic effect [9].

The facet joint nerve supply originates from two levels. One branch of the primary ramus arises from the nerve root at the same level as the joint and the second branch from the level above. For example, the facet joint between the L4 and L5 vertebral bodies is innervated by the medial branch nerves from the L3 and L4 nerve roots. In the lumbar region the medial branch of the posterior ramus lies in a groove at the base of the superior articular facet, where it lies in direct contact with the base of the superior surface of the transverse process, passing between the mammillary and accessory processes. The nerve passes under the mammillo-accessory ligament and this is the most reliable site for locating the nerve in the lumbar spine. The L5-S1 facet joint is innervated by three nerves, L4/L5, S1. Each medial branch of the posterior primary ramus also supplies the multifidus, interspinales, inter-transversarii mediales muscles, and the ligaments and periosteum of the neural arch [19,20].

Meticulous technique during lumbar facet RF denervation is important. Conventional RF treatment using a constant output of high-frequency electrical current produces controllable tissue destruction surrounding the tip of the treatment cannula and, when placed at precise anatomic locations, has demonstrated success in reducing a number of different chronic pain states [8]. It has also been occasionally used successfully in the treatment of acute radicular pain in patients who were not suitable for surgical treatment [8]. However, the data are scarce and anecdotal. Possible complications from RF denervation include bleeding, infection, nerve damage, broken electrodes, and post-denervation neuritis. A neuro-destructive method is, in principle, inappropriate for treating neuropathic pain [21,22]. Hence, a multi-discipline team including patient, doctor and care manager nurse shoud be involved in the shared decision making process of RF [23-25].

This study had several limitations, especially small sample size. We demonstrated a trend towards mild reduction in serum beta-endorphin levels after RF compared with NSAIDs, although the difference did not reach significance, likely due to this small sample size. Further larger scaled studies are necessary to confirm the role of beta-endorphins in RF denervation.

Conclusion

In this open label, randomized controlled clinical trial, RF lumbar facet denervation is an effective treatment modality for patients with LFS. RF lumbar facet denervation demonstrated a trend towards reduction in serum beta-endorphin levels.

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