

## Original Article

## Comparison of retrolaminar paravertebral infiltration of a non-steroid mixture with conventional epidural steroid infiltration in patients suffering from chronic radicular Pain- a retrospective study

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### Abstract

**Background:** Chronic radicular pain is often treated by epidural steroid infiltration (ESI). In 2014, the Food and Drug Administration (FDA) issued a letter warning that ESI may result in rare but serious adverse events, including “loss of vision, stroke, paralysis, and death”. In this retrospective study, we compare retrolaminar paravertebral infiltration (PVI) of a non-steroid-mixture with an epidural steroid injection (ESI).

**Materials and Methods:** We identified 31 patients registered in the Quebec Pain Registry suffering from chronic lumbar or cervical radicular pain referred to the Centre Hospitalier de l'Université de Montréal (CHUM) pain clinic between 2009 to 2014. These patients received ultrasound-guided retrolaminar PVI with a mixture of morphine 1 mg, ketamine 10 mg, neostigmine 0.5 mg, naloxone 2ng, and bupivacaine 10 mg. The control group, matched for gender, age, and DN4 sub-scale score at baseline, consisted of 31 patients with the same pathology; they were treated by fluoroscopic-guided ESI. Principal pathologies in both groups were disc disorders and/or foraminal stenosis. All patients received only one infiltration during the six months following the initial visit. The numerical rating scale (NRS-11) was assessed at the first visit and six months later. The BPI, PCS and SF-12 were compared in both groups. Overall satisfaction with pain relief after six months was assessed with a scale of 1 (very unsatisfied) to 6 (very satisfied).

**Results:** Average NRS-11 scores for the seven days preceding the first visit and after six months were compared in both groups. The same comparison was made for overall treatment satisfaction. There is no significant difference in the NRS-11 and in the satisfaction scores between the two groups.

**Conclusion:** Neither of the two methods was shown to be superior to the other in pain relief and overall treatment satisfaction after six months. Considering the possible complications and side effects of ESI, PVI with a non-steroid mixture might be considered as an alternative method. Possibly, multiple PVIs could further decrease pain. Well-designed studies are needed to evaluate this hypothesis.

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## Introduction

The first therapeutic epidural injection was performed in 1885 by neurologist James Leonard Corning by injecting the local anesthetic cocaine between the lower lumbar spinous processes. The first modern controlled trial evaluating epidural steroid injection (ESI) was performed by Swerdlow et al. in 1970. ESIs are the most widely used pain management procedures in the world. Their use is supported by many placebo-controlled studies and dozens of systematic reviews. Despite the extensive literature on the subject, there continues to be considerable controversy surrounding the safety and efficacy of this procedure (1).

ESI is the most frequently performed procedure in pain clinics throughout the United States, more than doubling between 2000 and 2008 (2). It is estimated that the annual cost to treat back pain alone exceeds \$100 billion (3). However, on April 23, 2014, the Food and Drug Administration (FDA) issued a drug safety communication warning that the injection of corticosteroids into the epidural space of the spine may result in rare but serious adverse events and required label changes to warn of rare, but serious neurological problems (4). Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. This warning resulted from a rapidly expanding body of the literature illustrating the potential for catastrophic neurological complications, including brain and spinal cord infarction following the intra-arterial injection of corticosteroids.

However, all experts did not accept this warning, and there is a debate regarding the risk-benefit of ESI (5). This controversy, along with the lack of sufficient supporting documents showing the ESI as an effective treatment in low back pain syndromes, caused us to consider other possible interventions with different medications. The purpose of this study is to compare the effectiveness of

ultrasound-guided retrolaminar PVI with a non-steroid containing mixture versus ESI in patients suffering from chronic cervical or lumbar radicular neuropathic pain.

## Methods

We identified two groups of 31 patients registered in Quebec Pain Registry data bank suffering from chronic lumbar or cervical radicular pain who were referred to the pain clinic between 2009 to 2014. Informed consent was obtained from all the patients. All the patients were 18 to 75 years old. The primary cause of the pain was a disc herniation or foraminal stenosis. The neuropathic nature of the pain was diagnosed based on the DN4 $\geq$ 4. All cases with malignancies, congenital anomalies, infection, motor or sensory neurological diseases, cognitive impairment, alcohol, or illicit drug dependence, and past history of lumbar or cervical operations were excluded. All patients were evaluated at the initial visit in the pain clinic and six months later. The patients received only one infiltration during the six months following the initial visit. The data were collected in forms completed by patients and/or a research nurse. Pain intensity was assessed at the first visit and at the six-month follow-up using a numerical rating scale (NRS-11). The BPI, PCS and SF-12 were compared in both groups. Overall satisfaction with pain relief over the six months was assessed with a scale of 1 (very unsatisfied) to 6 (very satisfied) (Statistical analysis software SAS version 9.3).

Using a Broad-spectrum convex transducer (C1-5-D), the case group received an ultrasound-guided (LOGIQ *e*, GE Healthcare, Milwaukee, WI) retrolaminar PVI with a mixture of morphine 1 mg, ketamine 10 mg, neostigmine 0.5 mg, naloxone 2 ng, and bupivacaine 10 mg. The vertebral laminae were identified by ultrasound imaging in a paramedian sagittal plane by sequentially visualizing transverse processes and the corresponding laminae (from lateral to medial). After local anesthesia with lidocaine 2%,

the block needle (BD spinal needle Quincke 25 G) was guided to contact the lamina, and the mixture injected was visualized under real-time imaging. The injection was done in the laminae adjacent to the root, which corresponds clinically and radiologically to radicular pain. Radiological images were verified for possible anatomical variations (such as lumbarization of S1 or sacralization of L5). The control group, matched for gender, age, and DN4 sub-scale score at baseline, consisted of 31 patients with the same pathology, pain, and period who were treated by ESI (interlaminar or foraminal) under fluoroscopic control.

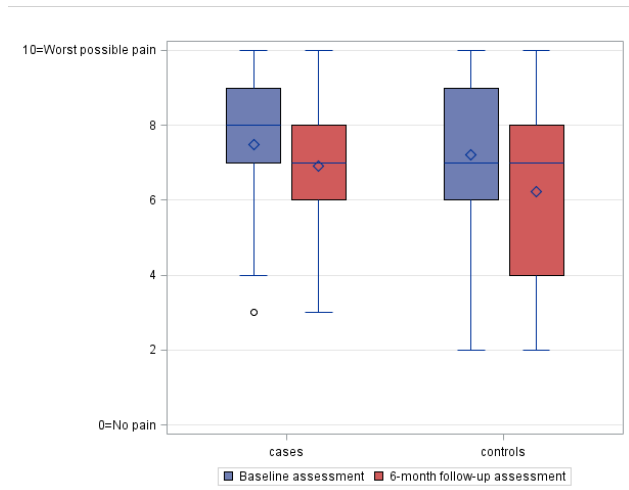
## Results

Average NRS-11 scores for seven days preceding the first visit were 7.5 (SD=1.7) and 7.2 (SD=1.9) in the case and the control groups, respectively. At the six-month follow-up visit, these scores were 6.9 (SD=1.9) and 6.2 (SD=2.4), respectively (Figure 1). No significant changes were noted in NRS-11 scores at the six-month visit between two groups. Overall satisfaction from pain relief at six months was 3.8 (SD=1.8) and 4.5 (SD=1.5) in the case and the control group, respectively (Figure 2). There was no significant difference in satisfaction score between the two groups.

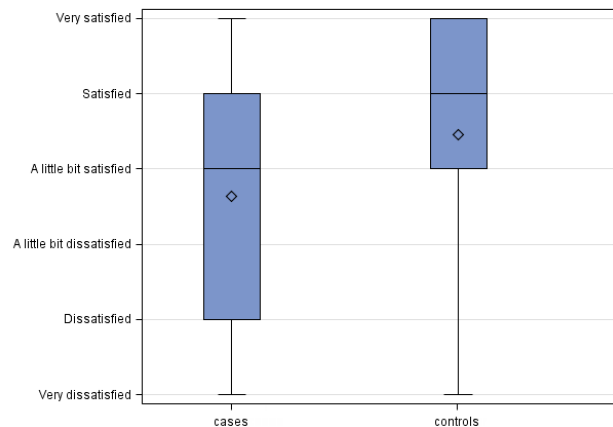
## Discussion

Based on the Crow W et al. study, it is estimated that the annual cost to treat back pain alone exceeds \$100 billion (3). Among those who develop low back pain, approximately 30% will develop either chronic pain or frequent recurrences. Neck pain is less well-publicized, but also exacts a steep socioeconomic toll. Nearly two thirds of patients will experience a significant episode of neck pain over the course of their lives, with the annual prevalence around 30%.

ESI could be considered as the most frequently performed procedures in pain clinics in the United States, and by some estimates, its use has doubled between 2000 and 2008 (2). Although this procedure has historically been utilized for spinal pain of all types, ESI is widely acknowledged to work better for

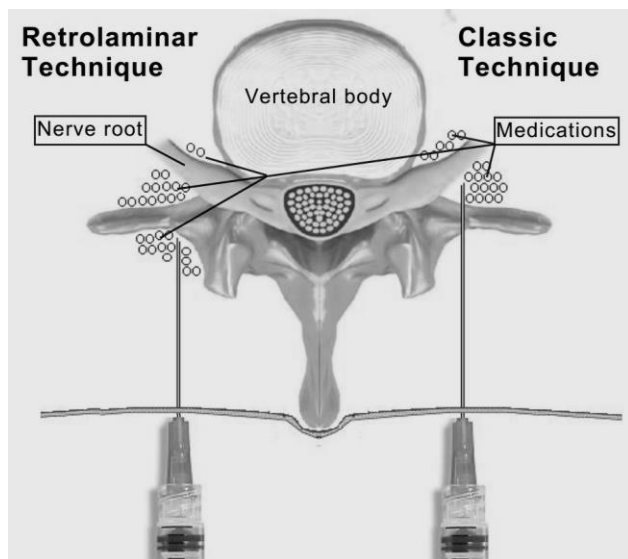


**Figure 1.** Average NRS-11 scores for the seven days preceding the first visit and at the six-month follow-up visit in the case and in the control groups (NRS-11: numerical rating scale).



**Figure 2.** Overall satisfaction from pain relief at the six-month follow-up visit in the case and in the control groups.

neuropathic pain. However, there continues to be enormous controversy surrounding the short- and long-term effectiveness and, more recently, safety of this treatment (4, 5). The mechanisms by which steroids produce their analgesic effects have been a subject of debate. Inhibition of phospholipase A<sub>2</sub> as an inflammatory mediator by itself (6) and as a rate-limiting factor involved in the production of eicosanoids (prostaglandins, prostacyclins, thromboxanes, and leukotrienes) could be the mechanisms of action. Steroids may inhibit pain via their ability to suppress ectopic discharges from



**Figure 3.** Schematic comparison of the retrolaminar and classic techniques of paravertebral blockade showing a transverse section of the vertebra.

injured nerve fibers (7) and depress conduction in normal unmyelinated C fibers. Other than the steroid effect, local anesthetics act via their increasing the blood flow in the ischemic nerves (8), suppressing ectopic discharges from injured neurons, slowing or halting nociceptive transmission (9), and the washout effect of the injected volume. There is increasing interest in the medical community in finding alternative approaches to treat back pain. First of all, retrolaminar paraspinal space could be considered as an alternative site for injection.

The thoracic paravertebral (TPV) nerve block technique was first described more than one century ago and reintroduced into clinical practice by Eason and Wyatt in 1978. Recently, there have been numerous reports concerning the use of an ultrasound guided paravertebral block. Interestingly, some authors have used ultrasound-guided retrolaminar technique (Figure 3) to infiltrate or to place the catheter (10). The concept that local anesthetic can penetrate the paravertebral space from a laminar injection challenges the classical teaching that the paravertebral space is defined posteriorly as a closed space by the costovertebral ligament. It is possible that the medication trickles through the medial aperture of the superior costovertebral ligament where the dorsal ramus of the spinal nerve exits posteriorly to innervate the paraspinal muscles. It is

also possible that the fluid tracks anteriorly through the loose tissues just lateral to the facet joints. The same concept could be considered to explain the diffusion of solution from the retrolaminar space to nerve roots in lumbar and cervical PVI. Moreover, the boundary of the TPV space in the caudal direction is subject to debate. Although some cadaver studies showed that the caudal end of the T12 TPV space is effectively sealed off by the origin of the psoas major muscle, other studies observed communication between thoracic and lumbar paravertebral space (11).

The feasibility of lumbar spine sonography has been reviewed by Darrietort-Laffite et al. In the cervical spine, Saranteas et al. examined the ultrasound anatomy of the cervical paravertebral space in 20 volunteers (12). They found that there was an excellent visualization of the C3, C4, C5, C6, and C7 transverse processes in all cases. The C5, C6, and C7 nerve roots were excellently identified in all cases. In the present study, all patients with cervical paravertebral infiltration received infiltration between C5 and C7.

The drug mixture we used consisted of morphine, ketamine, neostigmine, naloxone, and bupivacaine. In acute and chronic pain setting, morphine or its related family members are widely used. Its presynaptic and postsynaptic effects are via G-protein-linked opioid mu (mainly), delta, and kappa receptors. Presynaptic interaction inhibits the release of substance-P and calcitonin gene-related peptide by means of interactions with N-type voltage-dependent calcium channels and reduced calcium influx. Postsynaptic activation of opioid receptors leads to inhibition of adenylate-cyclase and also results in the opening of potassium channels, which in turn causes hyperpolarization, rendering the postsynaptic second-order neuron less responsive. Opioid receptors are expressed by central and peripheral neurons as well as by neuroendocrine (pituitary, adrenal), immune, and ectodermal cells (13). So morphine, which is used in the case group, might produce its analgesic effects via penetrating the epidural space and acting centrally and/or peripherally through an anti-inflammatory and analgesic effect on the peripheral nerves in the foraminal area.

Local anesthetics are primarily characterized by their ability to block voltage-gated sodium

channels. In addition, to sodium channel blockade, local anesthetics also interact with a wide array of alternative target structures, for example tetrodotoxin-resistant sodium channels, potassium channels, calcium channels, N-methyl-D-aspartate (NMDA) receptors, and G-protein coupled receptors (14). Other than blocking neural transmission, bupivacaine may possibly cause its analgesic effects in chronic pain via the other receptors and mechanisms.

Naloxone is an opioid mu-receptor competitive antagonist. In low doses (in fact, in “ultra-low doses”); it helps control pain and prevents hyperalgesia. A review of the literature suggests that under certain conditions, low-dose opioid antagonists (alone or in combination with opioids) can produce an antinociceptive or analgesic response (15). Furthermore, they have been used successfully in Crohn’s disease and irritable bowel syndrome (IBS) to control disease-associated pain. The possible mechanisms of action might be upregulation of opioid receptors, increased levels of endogenous opioids, decreased opioid receptor coupling to stimulatory G-proteins (mediated through filament A), and an inhibition of opioid agonist-induced activation of glial cells (15). In a case report, adding 50 ng/day naloxone to the intrathecal morphine infusion dramatically enhanced the analgesic effect of morphine without apparent side effects for more than three years (16). These mechanisms can explain partly the analgesic role of the naloxone in the mixture. The mechanistic rationale for the naloxone/morphine dose and concentration ratio was based on animal studies and a case report (16) in which an IT naloxone/morphine concentration ratio of  $1/10^5$  was efficient in controlling the pain for three years.

Ketamine is an intravenous anesthetic which has an analgesic effect in sub-anesthetic doses. In a review article, De Kock et al. (17) reviewed the effect of ketamine on the inflammatory process. They concluded that ketamine is an immunomodulator that prevents the exacerbation and the extension of local inflammation without blunting the local process and delaying inflammatory resolution. It has an anti-hyperalgesic effect due to its impact on NMDA receptors (18) and an anti-allodynic effect by suppressing toll-like receptor (TLR) mediated signal transduction (19). Ketamine possesses a plethora of

other actions that enhance its analgesic properties. These include blocking non-NMDA glutamate and muscarinic cholinergic receptors, facilitating GABA-A signaling, weakly binding to opioid receptors, and possessing local anesthetics as well as possibly neuroregenerative properties (20). Ketamine shows anti-inflammatory (17), antidepressant (21), precognitive (17) effects, as well as a beneficial effect on respiration, which can counter the side effects of morphine. Moreover, the beneficial effects of ketamine in the inflammatory process and post-operative outcome should not be neglected.

Neostigmine was introduced in 1931. It is a reversible inhibitor of the enzyme cholinesterase, which results in an increased concentration of the acetylcholine neurotransmitter. However, due to its hydrophilic nature (presence of a functional quaternary ammonia), it does not cross the dura mater. In 1933, Pellandra reported that intravenous administration of the anticholinesterase drug physostigmine produced analgesia in human beings. Neostigmine has been tested by the intrathecal (22), epidural (23), intra-articular (23), and intravenous (24) approaches to control pain. The analgesia resulting from spinal administration of neostigmine may be due to the increased concentration of acetylcholine and the consequent binding to muscarinic and nicotinic receptors. Epidural neostigmine analgesia seems to be a result of the more central rather than peripheral action. In a study by Lurreti GR et al. (23) in patients undergoing knee surgery, epidural neostigmine resulted in analgesia after the administration of a ten-fold lower dose (1  $\mu\text{g}/\text{kg}$ ) when compared to knee intra-articular administration, suggesting a central effect. Acetylcholine receptor activation in peripheral nerves is associated with analgesia (25), and intra-articular neostigmine seems to relieve pain after knee arthroscopy. Based on all these mechanisms, it could be hypothesized that neostigmine in the mixture could exert its analgesic effects by spreading on the dorsal root and probably in the epidural space. Due to very low doses of the drugs (especially the ultra-low dose of naloxone), absorption and systemic effects could not be an important factor in the long-term analgesic effect of the mixture.

The pain scores were relatively high in both

groups after six months. The score was only taken once by phone six months after the initial referral to the pain clinic. This score shows the average pain during the seven days before contact, but it does not show the intensity of pain in the days following injection. Overall satisfaction from pain relief is relatively high in both groups. So it can be concluded that the pain management service (including epidural or retrolaminar PVI) after six months had a positive impact on the pain intensity. Interestingly, there is no significant difference between two groups. However, there are the other limitations in this study such as: patient heterogeneity, the multicentric nature of the study, only one infiltration over six months, and missing information concerning pain relief in the days following infiltration.

## Conclusion

In order to better understand the outcome of patients treated via retrolaminar PVI using a new mixture, studies need to be undertaken involving a greater number of patients and randomized trials. It would be preferable to study a mixture of two or three drugs instead of five drugs as in the current study; the impact on pain and quality of life should then be evaluated at more frequent intervals. However, based on the FDA warning concerning ESI and the debate surrounding it, finding new approaches and medications for the treatment of spinal radicular pain is an important challenge that needs to be addressed in future studies. This study shows the possibility of using drugs other than steroids in paraspinal interventions.

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## Conflicts of Interest

The authors declare that they have no conflict of interest.

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