Effectiveness of Clonidine for the treatment of radicular pain: A randomized, double-blind and prospective study. (EFFOC study)

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1) To study the effect of Clonidine on lumbar radicular pain with a transforaminal epidural injection after 1 week, 1, 3 and 6 months using a BPI.2) To study the effect of Clonidine on lumbar radicular pain with a transforaminal epidural injection...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Spinal cord and nerve root disorders
Study type	Interventional

Summary

ID

NL-OMON37866

Source
ToetsingOnline

Brief title
EFFOC

Condition

- Spinal cord and nerve root disorders

Synonym
Radicular Pain, Sciatica

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Clonidine, Radicular pain, Transforaminal epidural injection

Outcome measures

Primary outcome

Changes of pain perception assessed with a Brief Pain Inventory (using NRS)

from pre-intervention compared with post-intervention (1hour, 1 week, 1 month,

3 months and 6 months)

Secondary outcome

Changes of function assessed with a Ostwestry Index from pre-intervention

compared with post-intervention (1hour, 1 week, 1 month, 3 months and 6 months)

Study description

Background summary

1.1. Radicular pain

It is estimated that 5-10 % of all patients with low back pain also have radicular pain in the lower extremities [1]. Many synonyms for lumbar radicular pain appear in the literature: sciatica, ischias, nerve root pain or nerve root entrapment. The annual prevalence of lumbar radicular pain is estimated at 2,2% [2]. Radicular pain is mainly diagnosed by history taking and physical examination. It is characterized by its radiation in a dermatomal pattern. There can also be sensory symptoms. Physical examination largely depends on neurological testing. The most applied investigation is the straight leg raising test (Lasegue). Patients with radicular pain may also show lower back pain, which is usually less severe than the pain in the leg. The diagnosis of radicular lumbar pain (sciatica) seems to be justified if a patient reports the typical radiating pain in one leg combined with a positive result on one or more neurological tests indicating nerve root tension or neurological deficit. The value of imaging techniques is still under debate, as in several studies on people with clinical symptoms of radicular pain it was not possible to verify their symptoms with MRI or CT scanning techniques [3]. However, it is customary

in studies assessing the effectiveness of a specific interventional therapy for radicular pain, to assess the spine with radiological imaging (MRI, CT) in order to quantify the extent of a disc extrusion beforehand [4,5].

1.2. Transforaminal epidural injection of corticosteroids as interventional treatment modality for lumbar radicular pain

Transforaminal epidural steroid injections are a well established, target-specific treatment modality for lumbar radicular pain. It is target-specific because it is a way to inject an anti-inflammatory agent in the ventral epidural space, right next to the dorsal root ganglion. In a recent systematic review [6] four randomized trials were included.
All of them could show pain relief in a period until 6 months (termed short-term). Only two of these studies could also indicate pain relief longer than 6 months. One study had as primary outcome, wether patients with radicular pain could avoid spine surgery [7] following transforaminal epidural steroid injections either with Bupivacaine alone or with Bupivacaine and Betamethasone (6 mg). 55 patients were randomized into one of the study groups. They were allowed up to 4 injections of the same study drug during the evaluation. Follow-up was between 13 and 28 months. At the end of the evaluation period 18 out of 27 patients receiving only Bupivacaine had chosen to undergo surgery. Of the 28 patients receiving the combination of Bethametasone and Bupivacaine, only 8 had undergone surgery.

Manchikanti et al [6] are giving the following indications for transforaminal epidural injections:
1. Intermittent or continuous pain causing functional disability;
2. Chronic low back and/or lower extremity pain resulting from herniated discs and radiculopathy, spinal stenosis and failed back surgery syndrome (FBSS);
3. Chronic low back and/or lower extremity pain which has failed to respond or poorly responded to non-interventional and non-surgical conservative management.

The most serious complications of transforaminal epidural steroid injections in the lumbar spine are related to neural and vascular trauma, intravascular injection and infection. Side effects related to the administration of steroids are generally attributed either to the chemistry or to the pharmacology of these substances.

1.3. Clonidine

Alpha-2-agonists have been in clinical use for decades, primarily in the treatment of hypertension. In recent years alpha 2 agonists have found wider application, particularly in the field of anesthesia and pain management [8]. Clonidine is the most widely used of the alpha 2 agonists. It has been used in the management of acute and chronic pain. Clonidine has been shown to provide benefit when utilized in plexus anesthesia, peripheral nerve blocks, as an adjuvant for epidural anesthesia and in the management of cancer pain. It is a

selective partial agonist for alpha-2-adrenoceptors, with a ratio of approximately 200:1 (α2 : α1) [9].

Alpha-2-receptors are G-protein linked receptors. When these receptors are activated, they exert their effects partly via the inhibition of cyclic adenosine monophosphate 3*,5*-monophosphate (cAMP) formation. Potassium channels also open, allowing the efflux of potassium from the neuronal cell, thereby resulting in cell hyperpolarization and decreased impulse transmission through affected nerve fibers. Yet another means by which this may occur is a decrease in calcium-channel dependent neurotransmitter release from affected neurons. Decreased calcium conductance via voltage-gated calcium channels may be responsible for this effect. This may also result in a diminished release of substance P.

Three subtypes of the alpha-2-receptor have been identified: alpha-2A, alpha-2B and alpha-2C adrenoceptors. 95% of the alpha-2 adrenergic receptors in the human dorsal root ganglia are of the alpha-2B and 2C subtypes [10]. In studies on rats where sciatic nerves were intentionally injured it was found that alpha-2-receptors were absent in normal nerves. Whereas alpha 2 receptors were found in the lesioned nerves due to the expression by recruited macrophages, lymphocytes and other immune cells. Peri-sciatic clonidine at the site of the nerve injury both prevents and reverses neuropathic pain [11].
This effect is associated with a reduction of the pro-inflammatory IL-1 and TNF in the sciatic nerve as well as with an elevation of the anti-inflammatory cytokine TGF-beta.
At the level of the dorsal root ganglion (DRG) acute mechanical compression of the DRG is sufficient to produce spontaneous activity in sensory afferents and to upregulate DRG mRNA and protein levels of proinflammatory cytokines.
In addition to the direct effects of DRG mechanical compression, herniated discs are perceived by the immune system as *foreign* and so induce a localized inflammatory response. Even in cases of contained herniation of a disc this inflammatory cascade can be induced by mere exposure of nucleus pulposus material to the DRG.
Proinflammatory cytokines, chemokines and the so called *inflammatory soup*(bradykinin, serotonin, PGE2 and histamine) can all enhance excitability of DRG neurons in normal rats, an effect that is greatly increased in neurons from rats with chronically compressed DRG neurons [12]

Study objective

1) To study the effect of Clonidine on lumbar radicular pain with a transforaminal epidural injection after 1 week, 1, 3 and 6 months using a BPI.

2) To study the effect of Clonidine on lumbar radicular pain with a transforaminal epidural injection after 1 week, 1, 3 and 6 months using the Ostwestry index

Study design

The design of the study is prospective and double-blind. It is going to be an injection of a medication to one of the lumbar or sacral dorsal root ganglions depending on the prior results of medical history and physical examination. All patients will have undergone radiological imaging of their spine before the intervention in order to assess the location and extent of the disc protrusion.

There are going to be two groups with 20 patients each:

- Group I will receive a standard treatment which is a combination of Ropivacaine 0.2% 2ml + Depomedrol 40 mg (i.e. 1 ml)
- Group II will receive a combination of standard treatment (Ropivacaine 0.2% 1.0 ml + Depomedrol 40 mg + Clonidine 150 mcg (i.e. 1.0 ml)

After inclusion each subject will be randomized to one of the study groups by our research nurse. The physician performing the intervention will be fully blinded to the combination of the medication. The total amount of medication is going to be 3 ml in each group.

Intervention

Control group: Transforaminal epidural steroid injection
Intervention group: Transforaminal epidural steroid injection with Clonidine

Study burden and risks

We verwachten een minimale belasting voor de patient omdat het om patienten gaat die sowieso kandidaten zijn voor een transforaminale epidurale injectie van steroiden. De injectie op een lokaal omschreven plek van Clonidine laat geen systemsiche effect verwachten - zoals b.v. bloedrukdaling
Als het na 3 maanden na de initiele interventie niet goed gaat met de pijn dan kan een gewone transforaminale steroidtoediening gedaan worden als "rescue" - onafhankelijk van de groep van de patient

We expect a minimal burden for patients who are included in the study. Patients who are included are all candidats for a transforaminal epidural steroid injection. From the injection of Clonidine in a circumscript area (i.e. Dorsal root ganglion) we expect minimal effect on cardiovascular parameters e.g. bloodpressure.
Next to their regular therapy (medication, TENS, fysiotherapy etc) patients who do not improve after our intervention are eligible for a "rescue" transforaminal epidural steroid injection 3 months after the initial intervention.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients with lumbar radicular pain and NRS > 4 for longer than 6 weeks;MRI evidence of a herniated disc

Exclusion criteria

Obesity (BMI > 40);Coagulopathy ;Use of anticoagulation;Systemic or local infection;Allergy to local anesthetics, clonidine or steroids;Legal claims or workman*s compensation;Pregnancy;FBSS ;Transforaminal epidural steroid injections or (pulsed) radiofrequency treatment at lumbar nerve roots within one year before inclusion in the study

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Clonidine
Generic name:	Clonidine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-09-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	25-09-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-003560-74-NL
CCMO	NL37710.058.11