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Treatment of Neuropathic Pain in Brachial Plexus Injuries

Nieves Saiz-Sapena, Vicente Vanaclocha-Vanaclocha, José María Ortiz-Criado, L. Vanaclocha and Nieves Vanaclocha

Abstract

Brachial plexus injuries are commonly followed by chronic pain, mostly with neuropathic characteristics. This is due to peripheral nerve lesions, particularly nerve root avulsions, as well as upper limb amputations, and complex regional pain syndrome (CRPS). The differential diagnosis between CRPS and neuropathic pain is essential as the treatment is different for each of them. Medical treatments are the first step, but for refractory cases there are two main types of surgical alternatives: ablative techniques and neuromodulation. The first group involves destruction of the posterior horn deafferented neurons and usually provides a better pain control but has a 10% complication rate. The second group provides pain control with function preservation but with limited effectiveness. Each case has to be thoroughly evaluated to apply the treatment modality best suited for it.

Keywords: brachial plexus injury, brachial plexus avulsion, chronic pain, neuropathic pain, deafferentation pain, phantom pain, pulsed radiofrequency, peripheral nerve stimulation, neuromodulation, DREZ-otomy

1. Introduction

Brachial plexus injuries are associated not only with motor and sensory functional impairment [1] but also with chronic pain in the affected upper limb [2–7]. Most of these injuries are due to motor vehicle accidents, particularly motorbikes [1, 5], but a few of them can occur
due to iatrogenia [8–16], particularly during lymph node biopsy [17, 18] or treatment of some malignancies [19].

The *pain* is chronic [20], persistent [7], constant [21], burning [22] and throbbing [17], with paroxysmal discharges [3, 6, 23], particularly upon gentle rubbing the affected area [4].

The *pain is distributed* in the distal areas of the upper limb, covering several dermatomes, mostly the caudal ones [24] and particularly the hand [5, 17, 23, 25]. The paroxysmal pain is felt in the arm [26]. Alldynia, hypersensitivity and electric-like discharges are present at the border between the normal and affected dermatomes [17, 26–29], particularly between T1 and T2, at the posterior aspect of the elbow [26].

The *pain severity* correlates with the magnitude of the brachial plexus injury [2, 3] and to the number of avulsed nerve roots [2–4, 21, 26, 30–33], particularly when the lower roots are affected [24, 34, 35]. Nevertheless, Bertelli et al. [21] found that in isolated C8 and T1 nerve root avulsions, there was no pain at all.

The *pain does not appear* immediately after the injury but a few days later [24] and no longer than 3 months after it [5, 6, 24, 26, 35, 36].

The *neuropathic pain can be associated with* phantom [37] or stump pain [38] in case of upper limb amputation, or to complex regional pain syndrome (CRPS) [6], inducing a complex pain condition rather difficult to control [19, 30, 31].

*Self-mutilation* has been described in 5–29% of obstetric brachial plexus injury cases [39, 40].

The *quality of life* is seriously impaired with sleep disorders, family troubles, unemployment, chronic depression and social withdrawal [2, 5, 6, 17, 21, 41–44]. Additionally, the chronic pain is a further hindrance to comply with a good rehabilitation programme, impairing a possible functional recovery [6, 45, 46]. Among all the disabilities induced by the brachial plexus injury, the pain has been found to be the symptom that most negatively affects the quality of life [47].

*Treatment* of this chronic pain can be troublesome, as the response to the different treatment modalities is poor and not all of them allow preservation of the remaining upper limb function [2, 5, 48].

### 2. Incidence

Although 50–82.7% of brachial plexus injuries suffer from chronic pain [2, 3, 5, 6, 17, 35, 49–51], it is severe in 41% of them [32]. The incidence and severity are higher in nerve root avulsions [2–4, 7, 21, 30, 33], especially when all the roots are avulsed [2, 17, 21]. Overtime there is a spontaneous progressive improvement, so just after the injury 90% of patients suffer from pain but affects only 30% of them 3 years later [35, 36, 49].

*Predisposing factors*: the strongest is alcohol abuse [17], but smoking [6, 17], other coexistent pain conditions [6], like psychiatric co-morbidities [6, 17], using a sling [5] and the marital status (both married or divorced versus being single) also increase the pain incidence [5]. A longer time using a sling increases the chance of chronic pain because limb movement restriction has a negative impact on recovery [5].
Brachial plexus injuries may also be accompanied by partial or complete traumatic upper limb amputation. About 50–85% of these amputees will suffer from chronic pain [52, 53] particularly in more proximal amputations [53]. This pain usually starts 1 month postamputation [53], and in 54–87% of them, it is followed by phantom limb pain [37, 53, 54]. This kind of pain is felt also in extensive nerve root avulsions, particularly when all of them are affected [55]. CRPS is present in 21% of brachial plexus injuries [6], and once it starts it is usually lifelong unless treated [35].

3. Pathophysiology

The neuropathic pain is induced by an injury to the somatosensory pathways [56, 57] like a brachial plexus injury, an upper limb amputation or both of them simultaneously [2, 7, 58].

The peripheral nerve injury induces deafferentation [2] and damage to the C nerve fibres [59]. The dorsal horn neurons devoid of their peripheral sensorial input start to fire spontaneously and erratically [60–64], stimulating pain sensation in the higher central nervous system levels [65, 66]. In experimental studies it has been found that the spinal cord microglia and astrocytes are activated at the injury site [67] and help to maintain the neuropathic pain [68–72]. Higher levels like the thalamus and the motor cortex also undergo the same process by which deafferented neurons create new synapses and reorganize and start firing in abnormal patterns [7, 73–77]. Descending pathways modulate the neuropathic pain [78] creating new circuits that induce and maintain it [79–81]. The brain and spinal cord neuronal reorganization leads to an increased sensitivity to otherwise normal stimuli, lowering the threshold required to feel the sensation as pain and inducing secondary hyperalgesia and allodynia [4, 82]. It also explains why the pain often extends beyond the denervated area [26, 33] and why it manifests at the border areas between the partially denervated and normal dermatomes [17, 27].

As mentioned above the pain seen after brachial plexus injury has two distinct patterns: paroxysmal and continuous. The first one is thought to originate from the deafferented posterior spinal horn neurons [60, 83], while the second one comes from the thalamus [74, 84]. In the phantom limb pain, the brain cortex undergoes a functional reorganization in response to the chronic pain [40, 85, 86]. Some have suggested that the neuropathic pain after brachial plexus avulsion is generated not by the avulsed nerve roots but by the remaining ones [67] that are also injured, although not so severely [34]. Although this might be true in some cases, it does not explain why the neuropathic pain severity is maximal when all nerve roots are avulsed [2, 17, 21, 55].

4. Medical treatment

This kind of pain, particularly in case of nerve root avulsions, is difficult to treat due to partial responses and frequent relapses [5, 6, 17]. The response to pharmacological treatments decreases when the pain intensity increases [6].
The non-steroidal anti-inflammatory drugs (NSAIDs) are of little help in the chronic phase [17, 30].

The first step is tricyclic antidepressants (TCAs) or serotonin and noradrenaline reuptake inhibitors [6, 57, 87]. Among TCAs, amitriptyline (25–125 mg/day) and venlafaxine (150–225 mg/day) are the most commonly used [6, 57]. They not only help with the pain but also with the accompanying nervous depression [57, 87]. A regular ECG surveillance is recommended as at high doses these drugs can induce cardiac arrhythmias [88]. Duloxetine, the most commonly used serotonin-noradrenaline reuptake inhibitor, is devoid of cholinergic or cardiac side effects [87].

The second step is the combination of the above-mentioned drugs with anti-epileptic agents [89], like gabapentin or pregabalin [6, 19, 27, 57, 87]. Clonazepam at night time is very effective, but it can induce drowsiness, and some patients find it difficult to tolerate [90]. Other anti-epileptic drugs like topiramate, carbamazepine, oxcarbazepine and lamotrigine are also used but with limited success [57].

Lidocaine (lignocaine) 5% patches applied to the painful area are the third line of medical treatment [27, 91, 92]. It controls the cold allodynia but not the mechanical one [73].

Capsaicin 8% patches are used but can cause severe local skin irritation [27].

Oral cannabinoids, which were successful in controlling brachial plexus injury pain in rats [70], have limited success in humans and are not currently recommended [93].

Opioids (tramadol [6, 89], morphine, oxycodone and tapentadol) are to be avoided as they are not very effective in the treatment of neuropathic pain [32] and because of their addictive properties [27, 57, 91, 92]. In any case the opioid dose should never exceed 180 mg/day of oral morphine equivalents [57] and should be complemented with TCAs and anti-epileptic drugs [89].

Other drugs have been tried experimentally in rats, like rapamycin [94], intrathecal Trichostatin A (TSA) [94] or intravenous immunoglobulin [95], but there are no reports of their use in humans.

Transcutaneous electrical nerve stimulation (TENS) has been used to control and prevent the development of neuropathic pain after brachial plexus injury [35, 96–98]. Its main advantage is that it can be self-applied by the patient. However, it needs constant application, and at times it can provoke local skin irritation [35, 96–98].

The common clinical features shared by neuropathic pain and CRPS hinder a pure clinical diagnosis [6]. Distinguishing between both of them is essential as the latter causes greater disabilities [99]. To differentiate them, an ultrasound examination can be performed, as the muscular architecture is preserved in neuropathic pain but not in CRPS [99].

Medical treatments can also classify the pain: stellate ganglion blocks will only relieve CRPS [6, 100, 101]. Other therapies for CRPS include botulinum toxin, which can be used to treat muscular trigger points [102] when found, and electroacupuncture, which has been found effective in controlling experimental brachial plexus pain in rats [103]. We have not found any publication reporting the use of electroacupuncture in human beings.
5. Surgical treatment

Brachial plexus injury repair by direct suture, by grafts or by nerve transfers, particularly sensory nerve transfers, minimizes the incidence and severity of neuropathic pain [4, 26, 34, 67, 104–109], and the sooner the repair is done the better [25, 67]. CRPS is the exception as further surgery outside trapped nerve decompression seems to have a negative impact on the outcome [101]. In these cases either an interscalene [102] or stellate ganglion block [110] or a cervical spinal cord stimulator [111–113] is recommended instead. The phantom limb pain only improves with central nervous system procedures [114, 115].

There are two main roads of action: neuromodulation and ablative procedures. The first group relies on applying electric impulses to different areas of the central or peripheral nervous system, aiming to block the transmission of the nerve impulses that are finally interpreted as pain in the sensory motor cortex. They are particularly effective for continuous pain but less so for paroxysmal painful discharges [84]. The ablative procedures aim to destroy the posterior horn spinal cord neurons that start to fire in an abnormal way after being disconnected from their peripheral sensory input [25, 64–66], controlling paroxysmal pain better than continuous pain [84].

5.1. Neuromodulation procedures

Peripheral nerve stimulation provides 50–83% pain relief in 65–80% of the patients [116–120], and the affected limb preserves the residual function remaining after the injury [121]. Allodynia and neuropathic pain are controlled with mild improvement in the sensory function [116, 118]. The results are stable long-term [118, 119, 121]. The electrodes can be implanted with an open surgical procedure [117, 119] or percutaneously under ultrasound guidance [116, 120]. Unfortunately lead fracture, displacement or infection can spoil an initial successful result [116, 120]. A further refinement is to apply the stimulating electrodes not through a cuff around the affected nerve but by direct selective nerve fascicle stimulation [122]. In this way only the affected sensory fascicles are stimulated and not the motor ones, improving the results and reducing the side effects, particularly muscle spasms [122].

Cervical spinal cord stimulation stops the transmission of the abnormal electrical impulses coming from the deafferentated posterior spinal cord horn neurons [123], controlling the pain with preservation of the remaining upper limb function [112, 124, 125]. Its success rate in the treatment of neuropathic pain associated with brachial plexus injuries is 50% [51, 111–113, 124–129]. It is particularly useful in CRPS [112] but it also helpful in nerve root avulsions [129]. In cases of failed previous dorsal root entry zone (DREZ), lesioning can provide good pain control [113]. Contrariwise, when the spinal cord stimulation failed the DREZ-otomy through radiofrequency, it yields suboptimal results [130]. Nevertheless several research groups recommend to restrict the cervical spinal cord stimulation for failed previous DREZ-otomy due to its high economical costs [25, 131–133]. A trial period is needed before the definitive pulse generator implantation to predict the results [129]. The stimulation parameters can be modified according to the patient’s individual needs through an external programming device. The electrodes can be implanted percutaneously or surgically. Lead fracture or dislocation...
and battery exhaustion will require surgical revision of the system. Some patients experience discomfort due to paresthesias particularly when rotating the head [111, 124]. This can be minimized by reprograming the active electrodes and the intensity of the electrical stimuli.

**Pulsed radiofrequency** has been reported in a few cases of brachial plexus injury including one with concomitant limb amputation, with a 60–70% pain improvement in a 6-month follow-up [38, 134]. The main advantage is that radiofrequency does not induce additional motor or sensory deficit, although the results are not long-lasting [135]. The data are insufficient to draw any definitive conclusions [38, 134, 135].

In small clinical series of patients, **deep brain stimulation** has shown a 55% improvement in neuropathic pain arising from brachial plexus injury and traumatic amputation pain [20, 58, 136]. After 1 year the effectivity is reduced in many patients, and increasing the intensity of the electrical stimuli is not always successful to improve the deteriorating results [20]. There is no agreement on where is the best target for the stimulation: some recommend the sensory thalamus [20, 58] and others the periaqueductal grey matter [137, 138].

In neuropathic pain induced by brachial plexus injury, **motor cortex stimulation** has shown a 42% effectiveness in controlling the continuous pain but no effectiveness for the paroxysmal discharges [84, 139]. A major drawback is the lack of factors to be able to predict the results to be expected [84]. This is particularly important considering the high cost and surgical risks involved in this technology.

### 5.2. Ablative procedures

The medial thalamotomy, the thalamic tractotomy, and the anterolateral tractotomy have been abandoned due to the limited pain control they provide and the side effects they carry [119].

The DREZ is an anatomical area of the spinal cord composed by the dorsal rootlets, Lissauers tract and the dorsal horn [25]. **DREZ-otomy** aims to destroy the neurons located in the posterior horn of the spinal cord that start firing abnormally once deprived of their peripheral sensory input [25, 140]. It has proved particularly effective in the control of brachial plexus-induced neuropathic pain [22, 23, 28, 48, 140, 141], but it is a destructive procedure that can be applied when no residual upper limb function has to be preserved (i.e. nerve root avulsions). It is particularly effective in controlling the paroxysmal pain but not so much in the constant aspect [23–25, 84, 133, 139, 142]. It provides a better pain control than the neuromodulation procedures, with a reported long-term success rates of 50–75% [22, 25, 29, 48, 143]. Unfortunately about 10% of patients develop ipsilateral leg weakness and ataxia [22–24, 28, 48, 133, 140, 141] due to the vicinity of the area to be lesioned to the motor corticospinal tract laterally and the dorsal column with proprioceptive information medially [25, 140]. This successful pain control correlates with an improvement in anxiety and depression and in a third of patients in returning to work [133, 144]. The pain improvement with this technique is independent of the time elapsed since the injury and the DREZ-otomy [25, 133]. Pain recurrence is expected in 13–20% of the patients [22, 23, 25, 28, 29, 132, 143, 145–147] particularly in those with constant type of pain [23, 24, 139] but with an acceptable pain control in over 60% of them [132, 143].
The recurrences seem to be more common in the first 12 months post-op and much rarer after 5 years of follow-up [48, 132]. Pain control and recurrences seem to be less common among nerve root avulsions than with other more peripheral brachial plexus injuries [143, 145]. Some surgeons have considered that a bad result would mean a DREZ lesion of insufficient size [25, 131] and used the intraoperative ultrasound imaging to guide the shape and size of those lesions [131]. They reported an initial 100% pain control that decreased to 87% on 47.5 months follow-up but at the price of a higher rate of lower extremity weakness and ataxia [131] (17%, compared to 10% in other patient series [22–24, 28, 48, 140, 141]). These results also reflect that apart from the spinal cord, there are other higher central nervous system areas involved in the generation and maintenance of the neuropathic pain induced after brachial plexus injury [148].

Lack of DREZ region damage confirmed in preoperative MRI seems to be an indicator of successful pain control with the DREZ procedure to the point that no patient with spinal cord dorsal horn abnormalities had a completely pain-free outcome [22]. It is suggested that if the posterior horn is abnormal, the thalamus will most likely develop deafferented neurons that will start firing in an abnormal pattern and thus the treatment should be directed there and not to the spinal cord [22]. This observation contradicts the fact that surgically amputated patients due to different medical conditions in whom a normal spinal cord anatomy is preserved fare worse with the DREZ operation than those that had a traumatic amputation [115]. In these DREZ-otomy failed cases, a cervical spinal cord stimulator is recommended [113]. Post-operative MRI examinations in radiofrequency DREZ lesions have shown that the surgically lesioned area extends beyond the posterior horn [149]. This is in concordance with the clinical fact that some patients develop post-operative leg weakness, ataxia and sensory abnormalities below the operated area [22–24, 28, 48, 133, 140, 141].

DREZ-otomy provides 83% pain control rate in phantom pain [115, 150, 151], 67% in burning pain and 29% for stump pain [115, 152]. Both amputation and nerve root avulsion phantom pain seem to benefit from DREZ-otomies [115, 150, 151]. The results in pain improvement are better in traumatic amputations than in those due to medical conditions [28, 115]. Some researchers recommend to start with neurostimulation in phantom limb pain and to recourse to the DREZ-otomy as a last resort [152].

The DREZ-otomy can be created microsurgically (Sindou’s technique) [25], with radiofrequency (Nashold’s technique) [29, 48], with laser [153–156] or even with an ultrasonic microprobe [131], but there are no major differences in pain control or patients’ quality of life between them [142, 156]. The microsurgical technique is performed with the regular bipolar forceps, which is less expensive than the other options (radiofrequency, laser, ultrasonic probe), making it ideal for countries with limited resources [144, 157]. Some scientists have attempted intraoperative neurophysiological monitoring to improve the clinical results [65, 158, 159]. Freeing the spinal cord completely helps to stop pain induction with neck movements [25]. A concern that has not yet been studied in detail is the possible long-term effects of extensive cervical laminectomies required for the procedure, as it might accelerate cervical kyphotic deformity with cervical spinal cord myelopathy [147]. In any case the original full bilateral cervical C5–T1 laminectomies [25, 140] have been replaced in many surgical units by hemi-laminectomies.
6. Conclusions

Brachial plexus injuries can be the source of chronic pain. This pain can be neuropathic, CRPS and/or phantom limb, particularly if there is extensive nerve root avulsion or an upper limb amputation. The pain is oftentimes excruciating and leads to a bad quality of life even interfering with the physiotherapy needed to achieve a good recovery. The response to treatment of this pain is not always as successful as expected. Some patients respond to medication, but many need neuromodulation or ablative procedures. The most effective surgical technique is the DREZ-otomy, but 10% of patients develop side effects. If the ablative procedures fail, cervical spinal cord stimulation can be attempted.

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