Dorsal Root Entry Zone Lesioning: Systematic Review

Lesionamento da zona de entrada da raiz dorsal: Revisão sistemática

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Abstract

Introduction Dorsal root entry zone (DREZ) leasioning (DREZ-otomy) is considered an effective treatment for chronic pain due to spinal cord injuries, brachial and lumbosacral plexus injuries, postherpetic neuralgia, spasticity, and other conditions. The objective of the technique is to cause a selective destruction of the afferent pain fibers located in the dorsal region of the spinal cord.

Objective To identify and review the effectiveness and the main aspects related to DREZ-otomy, as well as the etiologies that can be treated with it.

Methods The PubMed, MEDLINE and LILACS databases were used as bases for this systematic review, having the impact factor as the selection criteria. The 23 selected publications, totalizing 1,099 patients, were organized in a table for systematic analysis.

Results Satisfactory pain control was observed in 70.1% of the cases, with the best results being found in patients with brachial/lumbosacral plexus injury (70.8%) and the worst, in patients with trigeminal pain (40% to 67%).

Discussion Most of the published articles observed excellent results in the control of chronic pain, especially in cases of plexus injuries. Complications are rare, and can be minimized with the use of new technologies for intraoperative monitoring and imaging.

Conclusion DREZ-otomy can be considered a great alternative for the treatment of chronic pain, especially in patients who do not tolerate the side effects of the medications used in the clinical management or have refractory pain.

Keywords
- neuropathic pain
- dorsal root entry zone
- radiculopathy
- spinal cord

Resumo

Introdução O lesionamento da zona de entrada da raiz dorsal (*dorsal root entry zone*, DREZ), ou DREZ-otomia, é considerado um tratamento eficaz para a dor crônica decorrente de lesões medulares, lesão dos plexos braquial e lombossacro, neuralgia

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pós-herpética, espasticidade, entre outras lesões. O objetivo da técnica é causar uma destruição seletiva das fibras localizadas na região dorsal da medula espinal, entre elas as fibras aferentes de dor.

Objetivo Identificar a efetividade da DREZ-otomia e as principais etiologias que podem ser tratadas por este procedimento, e revisar os principais aspectos relacionados à técnica.

Métodos As bases de dados do PubMed, MEDLINE e Lilacs foram utilizadas na realização desta revisão sistemática, tendo o impacto como critério de seleção. As 23 publicações selecionadas, totalizando 1.099 pacientes, foram organizadas numa tabela para análise sistemática.

Resultados Controle satisfatório da dor foi observado em 70,1% dos casos, sendo que os melhores resultados foram encontrados em pacientes com lesão dos plexos braquial/lombossacro (70,8%), e os piores, em pacientes com dor neuropática do nervo trigêmeo (40% a 67%).

Discussão A maioria dos artigos publicados encontrou ótimos resultados no controle da dor crônica, principalmente na dor relacionada à lesão de plexos. As complicações são raras, podendo ser minimizadas com o emprego das novas tecnologias de monitoração intraoperatória e imagem existentes.

Conclusão A drezotomia pode ser considerada uma ótima alternativa para o tratamento da dor crônica, especialmente em pacientes que não toleram os efeitos colaterais das medicações utilizadas no manejo clínico ou apresentam dor refratária.

Palavras-chave
- dor neuropática
- zona de entrada da raiz dorsal
- radiculopatia
- medula espinal

Introduction

Neurosurgical procedures should be considered as a possible treatment for chronic pain refractory to pharmacotherapy and other treatments.[1] Over 100 million adults in the United States are afflicted with chronic pain conditions by different causes (chronic diseases, peripheral nerve disorders and primary pain disorders) that play an important role in the patient's quality of life.[2,3]

Chronic neuropathic pain seems like a disease in itself, without any benefit or protective significance that characterizes the role of nociceptive pain in the human body. This illness imposes economic burdens to individuals and society, which can be observed in studies that suggest that patients with chronic pain experience worse health-related quality of life than the general population.[4–6] Moreover, some epidemiological studies have also reported the negative effect that chronic pain has on health conditions, since it can be associated with more symptoms of anxiety and depression, and poorer sleep quality.[7]

The lesion of the dorsal root entry zone (DREZ) is considered an effective procedure to treat this type of pain. The goal of DREZ lesioning is to create a selective destruction of neurons and fibers that enter the DREZ and, by this mean, cut off the pain circuit and relieve the symptoms.[8] The idea for the DREZ operation came to be in the early 1970's, after the introduction of the gate-control theory by Melzack and Wall in 1965. It was discovered that electrical stimulation was able to reduce certain types of pain. Thus, it became clear that the modulation of DREZ was important to understand the pain mechanisms.[9] The first surgical attempts were made in 1972 to determine whether a destructive procedure in the DREZ was feasible, safe and effective. This procedure was described as microsurgical DREZ-otomy (MDT), and it consisted of an incision and bipolar coagulations performed ventrolaterally at the entrance of the rootlets into the dorsolateral sulcus. The lesion penetrates the lateral part of the DREZ and the medial part of the tract of Lissauer, extending down to the apex of the dorsal horn. The latter is recognized under the surgical microscope by its brownish-gray color. The typical lesion is 2 mm deep, and it is made at a 45° angle medially and ventrally.[10]

Recently, other types of DREZ-lesioning techniques have been described to better achieve the expected results regarding the symptoms of the patient symptoms. Hence, the aim of the present study is to clarify, by a literature review, the results with different DREZ operation techniques to treat conditions involving neuropathic pain.

Methods

The PubMed, MEDLINE and LILACS databases were searched for manuscripts related to the DREZ operation. All relevant articles were included in the present review. Additionally, the reference sections of these articles were evaluated, and papers that provided important information regarding the subject were included. The results and conclusion of these articles were summarized in a chart. All types of studies were accepted, including other literature reviews. Articles that did not provide data regarding the effectiveness of the technique were not included. The selection protocol followed the flowchart in ►**Fig. 1**.

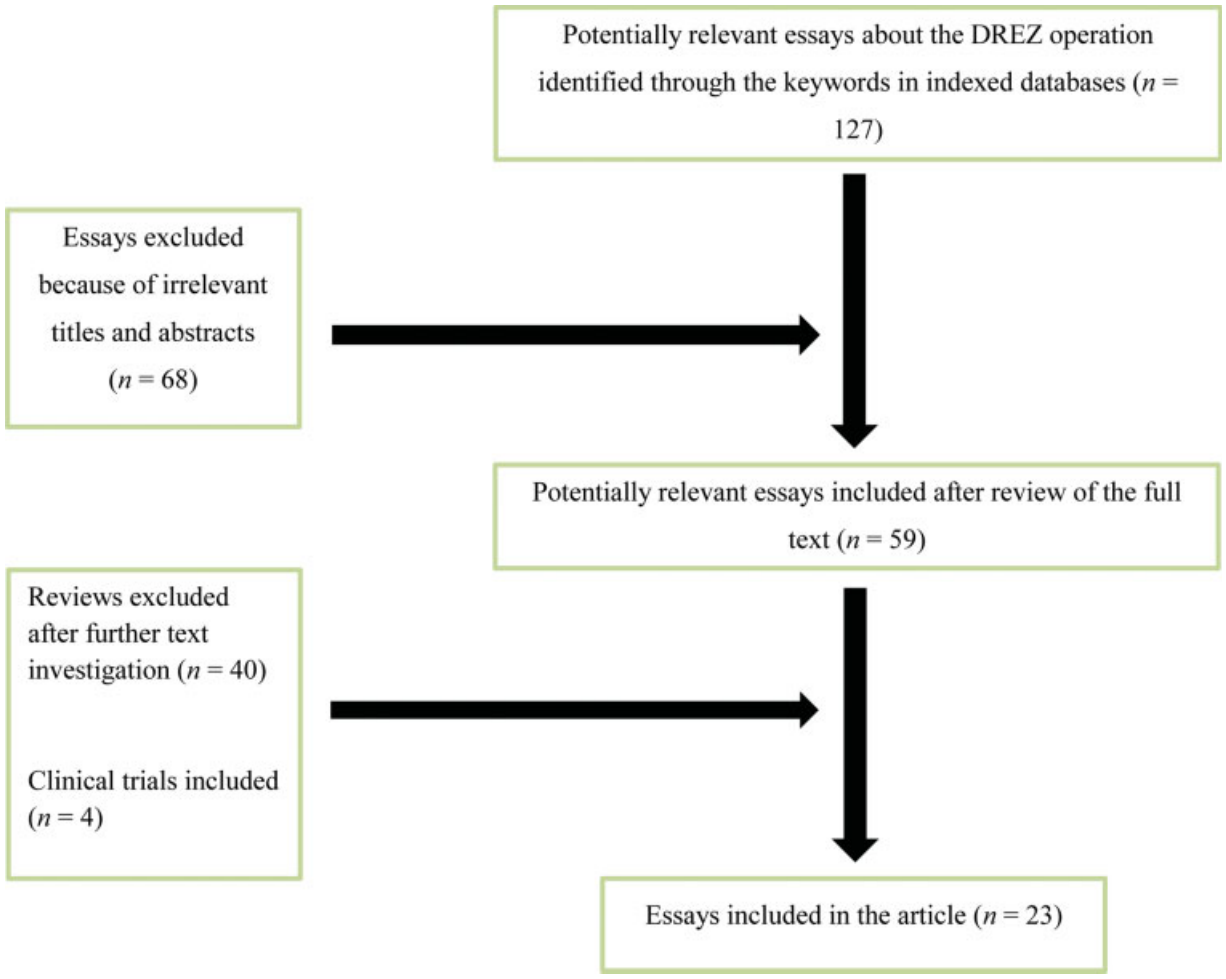

Fig. 1 Selection of articles.

Results

In total, 23 articles were included in the present review, totalizing 1,099 patients. The articles retrieved were written between 1986 and 2017. All data collected was summarized in ►**Table 1**, including the conclusion, year and number of patients evaluated.

Out of the 23 articles, 10 performed the procedure for the improvement of chronic pain related to spinal cord injury, 4, due to phantom pain, 13, due to lesion of the brachial or lumbosacral plexuses, 4, due to postherpetic neuralgia, 2, due to cauda equina lesion, 3, due to hyperspastic states, 3, due to facial pain of multiple causes, 3, due to peripheral nerves, 1, due to deafferentation pain syndromes, and 2 for the control of cancer pain (►**Table 1**).

For cervical DREZ lesioning, the highest percentage of good or excellent pain relief was found regarding cancer pain, hyperspastic states and cervical root avulsion. Plexus injuries, spinal cord injury, peripheral nerve injury and hyperspastic states were the etiologies related to the best results with conus medullaris DREZ lesion (►**Table 1**).

Nucleus caudalis DREZ lesion was the technique with the fewer number of patients ($n = 41$). All of them underwent surgery due to facial pain. The median percentage of good or excellent pain relief was of 60% (range: 40% to 73%). Due to the small sample, these results may not show the actual effectiveness (►**Table 1**).

Discussion

Considerations Regarding the Nonsurgical Management of Pain

There is a vast range of pharmacological and nonpharmacological treatments available, including different mechanisms to control the pain pathway. In general, the pharmacological treatment is well tolerated by the patients; nevertheless, some of those treatments have potentially complicated side effects.[11]

Antiepileptics, such as gabapentin and pregabalin, can be considered the most popular drugs to treat neuropathic pain. Pregabalin is approved for the management of pain due to diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia, and neuropathic pain due to spinal cord injuries.[11,12] Recently, the combination of intravenous ketamine and oral gabapentin was evaluated in a double-blinded, randomized, controlled trial on complicated neuropathic pain. This study showed an important improvement in pain scores in comparison to the placebo group.[13] Anticonvulsants, like phenytoin

Table 1 Systematic review of studies on lesioning of the dorsal root entry zone (DREZ)

Study	DREZ lesioning methods	Target	Etiology	Patients (n)	Pain relief
Friedman and Nashold, 1986[29]	Radiofrequency thermocoagulation	Cervix or conus medullaris	Spinal cord injury	56	50%
Saris et al., 1988[30]	Radiofrequency thermocoagulation, probe withe 0.5 mm of diameter, and 2 mm in depth	Conus medullaris	Phanton pain	9	67%
Young, 1990[31]	Radiofrequency method using a 0.5–2-mm stainless steel electrode with control of electric currentand duration	Cervix or conus medullaris	Brachial or lumbosacralplexuses injuries, spinal cord injury, phanton pain, postherpetic neuralgia,and cauda equina injury	21	67%
	CO2 Laser			20	45%
	Radiofrequency method usinga 0.25–2-mm stainless steel electrode with control of the electrodetemperature and duration			37	68%
Sindou, 1995[20]	Microsurgical DREZ-otomy, 45° ventromedially, and 2–3-mm deep	Cervix	Cancer pain	46	87%
		Conus medullaris	Cancer pain	35	78%
		Cervix or conus medullaris	Brachialplexus injuries, spinal cord injury, peripheral nerve lesion, phanton pain, postherpetic neuralgia	139	87%
		Cervix	Hyperspastic states	42	82%
		Conus medullaris	Hyperspastic states	93	
Bullard and Nashold, 1997[32]	Radiofrequency thermocoagulation	Nucleus caudalis	Facial pain	25	67%
Rath et al., 1997[33]	2-mm bare-tipped thermocontrolled electrode	Cervix	Cervical root avulsion	23	82%
		Cervix or conus medullaris	Spinal cord injury	23	48%
Samii et al., 2001[34]	Radiofrequency thermocoagulation	Cervix	Brachial plexus injuries	47	63%
Sindou et al., 2001[35]	Microsurgical DREZ-otomy, 3 mm in depth on average, with 35° of ventromedial obliquity	Cervix or conus medullaris	Spinal cord and/or cauda equina injuries	44	60%
Delgado-López et al., 2003[36]	Radiofrequency	Nucleus caudalis	Facial pain	5	40%
Sindou et al., 2005[37]	2-mm deep and made at a 45° angle medially and ventrally	Cervix	Brachial plexus injuries	55	66%
Spaic et al., 2005[38]	Microsurgical DREZ-otomy, 2-mm deep, and made at a 45° angle medially and ventrally	Thorax or conus medullaris	Spinal cord injuries	24	77%
				14	85%

Table 1 (*Continued*)

Study	DREZ lesioning methods	Target	Etiology	Patients (n)	Pain relief
	Microsurgical DREZ-otomy modifiedwith the dorsal horn suction				
Prestor, B. 2006[39]	Radiofrequency thermocoagulation	Cervix	Brachial plexus avulsion	26	96%
Chen and Tu, 2006[40]	Radiofrequency thermocoagulation	Cervix	Brachial plexus injuries	60	60%
Teixeira et al., 2007[41]	Radiofrequency lesions using a thermo-couple electrode spaced by 2 mm along the DREZ	Cervix	Radiation-induced brachial plexopathy	8	75%
Zhang et al., 2008[42]	Radiofrequency thermocoagulation	Cervix or conus medullaris	Deafferentation pain syndromes	23	74%
Hong et al., 2008[43]	2.5-mm deep radiofrequency electrode at in the Lissauer tract and obliquely oriented at 45°	Cervix	Upper-extremity spasticity	9	67%
Kanpolat et al., 2008[44]	Radiofrequency electrode at 45° and 2-mm depth to the spinal cord	Cervix or conus medullaris	Brachial plexus avulsion, phantom limb pain, painful spasticity after spinal cord injury, tumor and postherpetic neuralgia	44	77%
		Nucleus caudalis	Facial pain	11	73%
Ruiz-Juretschke et al., 2011[45]	Radiofrequency thermocoagulation	Cervix	Spinal cord injury, brachial plexus avulsion and other peripheral nerve injuries	13	77%
		Thorax and conus medullaris		6	50%
Awad et al., 2013[46]	Radiofrequency thermocoagulation	Cervical	Brachial plexus injuries, spinal cord injuries	19	69%
Haninec et al., 2014[47]	Radiofrequency electrode with a tip 2 mm deep	Cervix	Brachial plexus injury	48	70.8%
Liu et al., 2015[48]	Microsurgical DREZ-otomy assisted with spinal cord stimullation	Thorax and conus medullaris	Postherpetic neuralgia	6	83%
Chivukula et al., 2015[49]	Radiofrequency thermocoagulation	Nucleus caudalis	Facial pain	16	68.75%
		Cervix	Brachial plexus injury and postherpetic neuralgia	25	44%
		Thorax and conus medullaris	Postherpetic neuralgia, spinal cord injury, phantom limb and pelvic pain	42	71.40%
Takai and Taniguchi, 2017[23]	Microsurgical tumor forceps with ablunt dissection technique at a depth of 4–5 mm from thesurface of the DREZ.	Cervix	Brachialplexus injuries	10	90%

and carbamazepine, and other older-generation antiepileptic drugs (phenobarbital and valproic acid) have unfavorable metabolic and interaction profiles; thus, they are being less and less prescribed nowadays.[14]

Tricyclic antidepressants can modulate afferent pain pathways by increasing the levels of serotonin and norepinephrine in the central nervous system. Tricyclics have proven to be effective in the treatment of several chronic pain conditions, and can also be considered a first-line treatment in patients with neuropathic pain. Although these medications tend to be well-tolerated, various side effects are described, which are caused by the serotonergic, noradrenergic, and anti-histaminergic properties of these drugs. These adverse effects include: bladder retention, prolonged QT interval, sedation etc.[15]

Cannabinoids have received a lot of attention in recent years. This is due to studies that have shown their analgesic effects for non-cancerous pain. While cannabinoids tend to be well-tolerated with mild, transient side effects, more studies are required to prove the effectiveness and security of these drugs for the treatment of neuropathic pain.[16,17]

Surgical Treatment

Lesioning of the DREZ is a well-established surgical treatment for neuropathic pain. This procedure can be considered effective, safe and well-tolerated by most patients, justifying its frequent use.

Since the first description, DREZ lesioning evolved considerably. Created as a method for pain control for patients with chronic pain following brachial plexus avulsion, it can be used for many conditions, such as deafferentation pain, postparaplegia pain, painful spasticity, facial pain, cancer pain, postherpetic neuralgia, and brachial and sacral plexus avulsions.

The effectiveness of DREZ lesioning is based on the physiopathology of these diseases. They have in common neuropathic pain, which can be caused by imbalances between excitatory and inhibitory somatosensory signaling, alterations in ion channels, and variability in the way that pain messages are modulated in the central nervous system.[18]

The dorsal root of the spinal cord contains the axons from the primary afferent fibers originated in nociceptive receptors, which are responsible for the connection between the peripheral nervous system and the central nervous system. These neurons can ascend or descend a few vertebral levels through the tract of Lissauer. They enter the spinal cord through the dorsal root, where neurotransmitters are liberated, activating the second-order neurons located in the dorsal root. The second-order neurons ascend in the spinal cord through the lateral spinothalamic tract and spinal lemniscus until they reach the primary somatosensory cortex, where the information is processed. Considering these anatomophysiological aspects, it is simpler to understand why the destruction of the dorsal root has the potential to modulate neuropathic pain.

However, DREZ lesioning does not affect only pain fibers. The procedure has the ability of interrupting the unmyelinated and small myelinated fibers (considered tonigenic by their nociceptive input), as well as the large myelinated fibers going to the ventral horn, which are situated laterally and centrally in the DREZ respectively. At the end, the targets for lesioning are the central portion of the dorsal rootlets, the lateral part of the tract of Lissauer, and mainly the first five dorsal layers of the dorsal horn, where the (deafferented) hyperactive neurons are located (which are involved in the physiopathology of neuropathic pain) or where the excitatory segmental circuitry of tone is situated (which is involved in spasticity) .

Fig. 2 Vessels along the sulcus.

The procedure is performed in prone position, and, depending on the level of the spinal cord, it may require a three-point cranial fixation device to align and immobilize the spine and skull.[19] The laminectomy level should be determined based on the symptomatology, which generally follows specific dermatomes, demanding the bilateral destruction of fibers. Hemilaminectomies can be used for postherpetic neuralgia, or less frequently for single-dermatome pain or unstable spine. Patients undergoing a conus medullaris DREZ generally have laminectomies from levels D10 to L1, while patients undergoing nucleus caudalis or solitarius lesions undergo a small suboccipital craniectomy and Cl-C2 laminectomies.[19]

The dura mater and arachnoid are opened in the midline. Some structures, like the serpiginous vessels (►**Fig. 2**), may be present along the sulcus, so they must be retracted to enable a proper visualization of the region. Once the DREZ is located (►**Fig. 3**), the electrode can be introduced. Radiofrequency lesions are generally made at 75°C for 15 seconds, at 1 mm intervals along the intermediolateral sulcus, including the entire altered zone. The electrode should penetrate 2.0 mm deep and be held at a 25° angle into the dorsal nerve rootlet (►**Fig. 4**). The

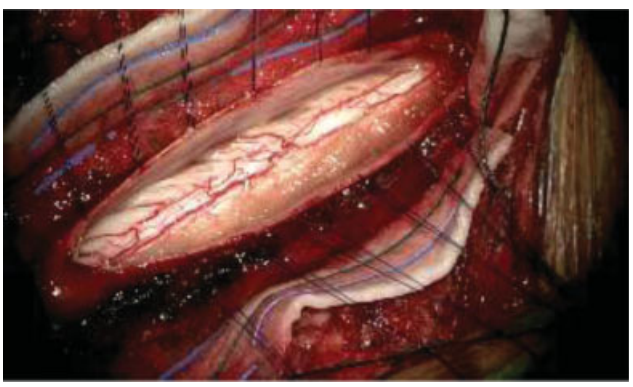

Fig. 3 Delimitation of the posterior medial sulcus (PMS).

Fig. 4 DREZ lesioning using the electrode.

procedure is extended to the segments corresponding to the pain territory, including one level above and one below.[20]

Takai and Taniguchi[23] described a posterior horn lesion using a microsurgical tumor forceps with a dissection technique at a depth of 4 mm to 5 mm from the surface of the DREZ. This new technique is based on recent findings regarding neuropathic pain suggesting the involvement of deeper layers of the gray matter of the spinal cord in pain conduction.[22] This justifies the performance of deeper lesions on the posterior horn.

Another interesting fact regarding DREZ lesioning is the worse results found in conditions with diffuse pain. This seems to be related to the delimitation of the appropriate lesion level, which can be difficult depending on the case. Chun et al.[21] described a modified DREZ lesioning procedure performed on both the complete injury zone (directly-injured cord level following spine injury) and the incomplete injury zone (indirectly-injured cord level identified on magnetic resonance imaging by signal change). This technique showed better results for diffuse pain than the original one, so they concluded that DREZ lesioning should be performed from the injured level up, including all abnormal rootlets above the level of the injury.

Sindou and Jeanmonod[24] reported a series of 53 patients with harmful spasticity in one or both lower limbs. These patients underwent MDT for their painful state or abormal postures (either hyperextention or flexion). Spasticity and spasms decreased or were abolished in most patients, 75% and 88.2% of them respectively. Abolition of sensation was found in less than 10% of the patients. This study showed that MDT has the potential to significantly improve the quality of life of the patients. In 2017, Sitthinamsuwan et al.[25] Published a study comparing DREZ lesioning and selective dorsal rhizotomy in fifteen spasticity patients. They concluded that DREZ lesioning is more effective to reduce spasticity, but more destructive than selective dorsal rhizotomy. Due to this, they suggested that DREZ lesioning should be preferred for bed-ridden patients, white selective dorsal rhizotomy, for ambulatory patients.

In 2016, Sindou and Georgoulis[26] published a case series of 3 patients with focal dystonia who underwent cervical microsurgical DREZ-otomy. They noticed that all patients maintained the relief of hypertonia, the sustained abnormal dystonic postures remained absent, and most of the functional benefit was still present at the last follow-up. No patient suffered total loss of tactile sensation and proprioception. However, thermal and nociceptive sensations almost disappeared in all three patients. Moreover, patients did not develop neuropathic pain.[26]

The complications associated with DREZ lesioning can be separated into two different groups: over-lesioning and under-lesioning. The most common complications regarding over-lesioning are paralysis and dysesthesia, due to the destruction of adjacent pathways in the spinal cord (the lateral corticospinal, rubrospinal and spinocerebellar tracts, and the dorsal fasciculus). Genito-sphincterian deficits are another possible complication.[19] On the other hand, ineffective pain control represents the under-lesioning complications.

To minimize the complications, it is imperative to choose the right spinal cord level, size of the lesion and angle of insertion. Henssen at al.[27] conducted a study in 2019 to measure the angle between the DREZ and the posterior median sulcus (PMS). They made 11.7-T post-mortem magnetic resonance images and compared them to polarized light imaging microscopy to determine the fiber orientation of the dorsal horn tracts. The median angles between the DREZ and the PMS were of 40.1° (left hemicord) and 39.8° (right hemicord). With these results, they concluded that an insertion angle of 25° should be recommended for DREZ lesioning.

Another study, conducted in 2019 by Monaco et al.,[28] described a real-time imaging technique to optimize DREZ lesioning using intraoperative ultrasound (US), which can determinate the exact location of the gray matter and dorsal horn. The US enables a correct positioning of the needle during the puncture, a proper angular adjustment, and a controlled depth.

Conclusion

Lesioning of the DREZ is an effective and safe procedure that should be considered a treatment for neuropathic pain due to diverse etiologies. Even though the pharmacological treatment is a possibility for the non-complicated cases, the surgical procedure is related to better results and fewer side effects. Thus, the treatment must be individualized, considering the quality of life and the decision of the patient.

Conflict of Interests
The authors have no conflicts of interest to declare.

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