

# Treatment of phantom pain with contralateral injection into tender points: a new method of treatment

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## Objective

The aim of this study was to ascertain the existence of contralateral painful muscle areas mirroring phantom pain and to evaluate the short-term effects of anaesthetics versus saline, injected contralaterally to control phantom and phantom limb pain.

## Design

This was a double-blinded cross-over study.

## Participants

This study included eight lower-limb amputees with phantom limb pain in the past 6 months.

## Interventions

Either 1 ml of 0.25% bupivacaine or 0.9% saline was injected alternately in each point with a 28-G needle, with 72 h between injections. The main outcomes measured were phantom sensation modification and the intensity of phantom limb pain (visual analogue scale) before and after injections.

## Results

Painful muscle areas in the healthy limb do not mirror the topographical distribution of phantom limb pain. At 60 min after the injection, a statistically significantly greater relief of phantom limb pain was observed after using a local anaesthetic compared with that when using saline injection ( $P = 0.003$ ). Bupivacaine consistently reduced/abolished the phantom sensation in six out of eight patients. These effects on phantom sensation were not observed after saline injections.

## Conclusion

Contralateral injections of 1 ml of 0.25% bupivacaine in the myofascial hyperalgesic areas attenuated phantom limb pain and affected phantom limb sensation. Our study gives a basis of a new method of management of that kind of severe pain to improve the method of rehabilitation of amputee. However, further longitudinal studies with larger number of patients are needed to confirm our study.

## Keywords:

hyperalgesic areas, phantom pain, phantom sensations

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## Introduction

Phantom limb pain has been reported to occur in up to 90% of limb amputees [1]. Despite such a high prevalence of this problem and a wide variety of treatment approaches that have been used, mechanism-based specific treatment guidelines are yet to evolve [2,3]. The nonpharmacological or local modalities used for treating phantom pain range from invasive procedures such as spinal surgery [4,5] to less invasive treatments such as electrotherapy [6], acupuncture [7] and the use of local anaesthetics [8].

To alleviate phantom pain, acupuncture needs to engage the nervous system to override the response to mismatched information. Acupuncture to the intact limb sends a normal afferent input to the nervous system, eliciting an analgesic effect. Acupuncture stimulation of points in the ear, stump, scalp and contralateral limb has been reported to help alleviate symptoms in individuals with phantom limb syndrome [9–11].

Moreover, contralateral painful muscle areas (i.e. in the intact limb) and a phenomenon called synchiria have been reported. Contralateral painful muscle area is related to the areas of pain felt in the phantom [12], whereas synchiria is defined as the perception of touch on the phantom on the reflected intact limb [13].

These clinical observations suggested the idea that to treat these painful spots in the healthy limb by means of other physical treatments such as transcutaneous electrical nerve stimulation (TENS) [14], as well as with locally injected anaesthetics, would influence the phantom pain sensation of the contralateral ones. As far as we know, although positive results were obtained using anaesthetic injection on contralateral muscle

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painful areas, there are only a few case reports dealing with this possible treatment [12,15–17].

Experimental observations support the hypothesis of a potential central origin of these seemingly heterolateral and reciprocal responses. The functional bilaterality at the spinal and higher supraspinal levels would then lead to mixed short-term responses both in the sensory and in the motor compartments [18,19].

Treatment of phantom pain can be classified as medical, nonmedical and surgical. Medical treatment is the most effective. Numerous medical interventions have been proposed over the years, but tricyclic antidepressants and sodium channel blockers are currently considered to be the drug treatments of choice for neuropathic pain [20].

Selective serotonin reuptake inhibitors [21] and benzodiazepine clonazepam have been reported to have a beneficial effect [22]. However, there is a general clinical impression that benzodiazepines do not produce substantial pain relief. Carbamazepine, an anticonvulsant drug, has been reported to be effective in the treatment of phantom pain [23]. Novel anticonvulsants such as lamotrigine and gabapentin may also prove to be effective in phantom pain [24].

Nonmedical treatment can be combined with medical treatment and various noninvasive techniques such as TENS, vibration therapy, acupuncture, hypnosis, biofeedback and electroconvulsive therapy. Despite the widespread use of some of these techniques, clear evidence of effect is limited [25].

Surgical treatments in the form of stump revision or neurectomy, cordotomy, thalamotomy and sympathectomy for phantom pain has been attempted for decades, but the results have generally been unfavourable [26].

### Aim

The aim of this study was to verify the existence of these contralateral painful muscle areas mirroring the painful areas of the phantom and evaluate, in the short-term, the effects of anaesthetics versus saline injection in the contralateral painful muscle areas in the control of phantom and phantom pain.

### Patients and methods

After the approval of the protocol from our ethical committee and after providing detailed information to the patients as regards the aim and procedures of the study, eight lower-limb amputees affected by

phantom limb pain lasting for more than 6 months gave their consent and were then enrolled in this study. Demographic features of the study group are described in Table 1. Exclusion criteria were the presence of stump pain, nonhealed early surgical scars or ulcers of the stump and the concomitant presence of polyneuropathy. The aetiology of amputation was traumatic (three cases) and vascular (five cases).

### Clinical assessment

Patients were requested to draw on a paper their phantom and the painful sites within the phantom. Thereafter, on the healthy limb, painful muscle areas were searched by palpation on the corresponding topographical areas, according to Travell's manual semeiology [27]. Painful muscle sites to palpation were reported on paper and also marked on the skin of the patients (Fig. 1).

The same physician who performed the basal clinical examination, blinded to the type of treatment performed, visited the patient collecting the number of painful muscle areas present within 1 h after the injection. The intensity of the phantom pain was evaluated before and after treatments by means of visual analogue scale from 0 (no pain) to 10 (worst pain ever experienced).

### Treatments

In a double-blind cross-sectional way, a saline or a long-lasting anaesthetic (bupivacaine 2.5 mg/ml) was prepared in a separate room by a nurse by filling syringes of the same size (10 ml), attached to 28-G needles, to allow the injection of the same volume of 1 ml of saline or anaesthetic at each point. An independent doctor performed the injection of all signed points by injecting 1 ml of the given solute, blinded to the contents of the syringe and on the aim of the study.

### Randomization

All patients were injected with both saline and anaesthetics with a cross-over design (Table 2). Treatments lasted from each other not less than 72 h.

**Table 1 Demographic data**

Age $\pm$ SD (years)	70.1 $\pm$ 7.7
Sex (male/female)	6/2
Level of amputation	Above the knee
Side of amputation (left/right)	5/3
Duration of phantom pain (months)	>6
Cause of amputation	
Traumatic	3
Vascular	5

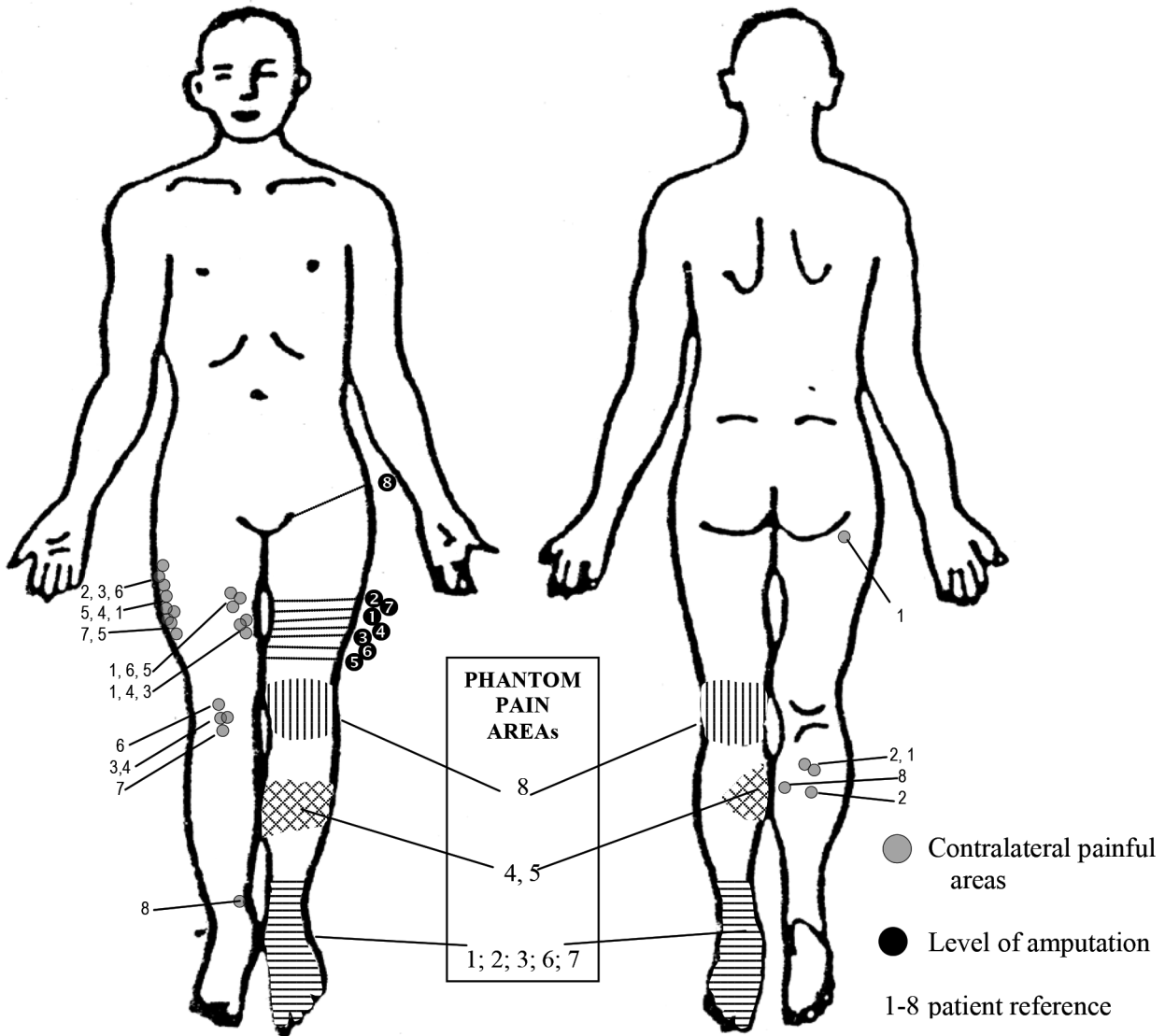
**Results**

**Phantom pain**

No statistically significant differences were found on comparing the basal values of phantom pain

before treatments (saline-basal vs. bupivacaine-basal;  $P = NS$ ). In addition, no statistically significant difference was found in phantom pain values in the two groups between the first and the second treatment (Table 2 and Fig. 2).

**Figure 1**



Representation of painful areas, level of amputation and phantom pain areas. Numbers from 1 to 8 represent the patients. Transverse striations above the knee represent levels of amputations. Striated areas at the knee and below represent painful areas on the amputated side.

**Table 2 Pain features**

	Patients								Mean ± SD	P value
	I	II	III	IV	V	VI	VII	VIII		
Number of painful spots	5	7	5	4	6	8	3	4		
Randomization group	SAL/BUP	SAL/BUP	SAL/BUP	BUP/SAL	BUP/SAL	BUP/SAL	SAL/BUP	BUP/SAL		
Pain BS										
Mean	8.3	9.0	6.6	7.7	7.1	8.0	7.8	7.9	7.8 ± 0.7	
SAL	8	8.8	6.5	7.8	7.2	7.7	7.8	7.6	7.7 ± 0.7	NS
BUP	8.5	9.1	6.7	7.5	7	8.2	7.7	8.1	7.9 ± 0.8	
1st trial	8	8.8	6.5	7.5	7	8.2	7.8	8.1	7.7 ± 0.7	NS
2nd trial	8.5	9.1	6.7	7.8	7.2	7.7	7.7	7.6	7.8 ± 0.7	

BS, basal values; BUP, bupivacaine 2.5 mg/ml; SAL, saline.

At 1 h after bupivacaine treatment, a significant reduction in the phantom pain versus basal values ( $P < 0.0005$ ) was found. Saline also induced a significant decrease in the phantom pain versus basal values, with a lower level of significance ( $P < 0.05$ ). Decrease in pain after bupivacaine is significantly more compared with that after saline ( $P < 0.005$ ) (Table 3 and Fig. 3).

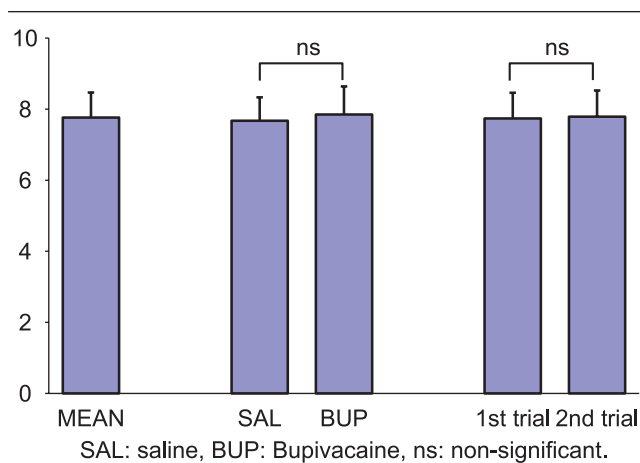
Figure 2 shows no statistically significant differences on comparing basal values of phantom pain before treatments (saline-basal vs. bupivacaine-basal;  $P = NS$ ), as well as in phantom pain values in the two groups between the first and the second treatment.

**Phantom sensation**

Bupivacaine consistently reduced/abolished the phantom sensation in six out of eight patients. These effects were not observed after saline injections.

Figure 3 shows significant reduction in the phantom pain versus basal values. Saline also induced a significant decrease in the phantom pain versus basal values, with a lower level of significance ( $P < 0.05$ ). Decrease in pain after administration of bupivacaine was significantly greater compared with that after administration of saline ( $P < 0.005$ ).

**Figure 2**



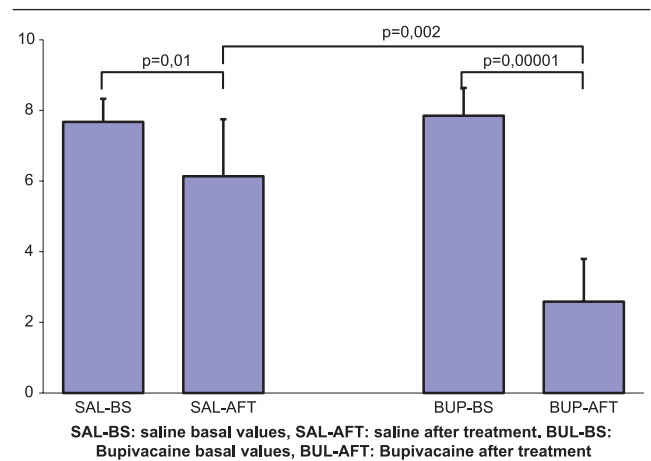
Comparison of basal phantom pain values (visual analogue scale). BUP, bupivacaine; SAL, saline.

**Discussion**

The presence of continuous intractable pain is a serious bias to the rehabilitation of amputees, and it affects the outcome of these patients in terms of speed of recovery, prosthesis fitting and quality of life [2,28]. From the literature emerges a new landscape where almost all of the 68 methods of treatment mentioned in a review of the 80s are reported as successful by some authors and unsuccessful by the others [29]. Unfortunately, until now there is no clear consensus about the efficacy of phantom limb pain treatment [30] and the situation seems to be very much the same as that critically described by Sunderland [31] that any operation selected for phantom pain seems to be more likely to fail than to succeed.

A part of the therapy focused on the amputated limb (mainly on the stump pain). The obvious lack of a physical area where we can locally apply physical treatments has forcefully directed the attention of clinicians to the possible utilization of the contralateral healthy limb to apply physical therapies. This possibility has found some other justification in the observations that hyperalgesic muscle areas are present in the healthy limb and that cutaneous stimuli applied to one limb can evoke simultaneous sensation in the

**Figure 3**



Pain variation 1 h after treatment. BUL-AFT, bupivacaine after treatment; BUL-B, bupivacaine-basal values; SAL-AFT, saline after treatment; SAL-B, saline-basal values.

**Table 3 Pain modification 1 h after treatment**

Treatment	Patients								Mean ± SD	P value
	I	II	III	IV	V	VI	VII	VIII		
SAL-B	8	8.8	6.5	7.8	7.2	7.7	7.8	7.6	7.7 ± 0.7	-
SAL-AFT	5	8.2	3.2	6.5	7	7.7	6.2	5.3	6.1 ± 1.6	0.01024
BUP-B	8.5	9.1	6.7	7.5	7	8.2	7.7	8.1	7.9 ± 0.8	-
BUP-AFT	3	2.1	3	2.6	2.5	4.1	0	3.4	2.6 ± 1.2	0.00001

AFT, after treatment values; B, basal values; BUP, bupivacaine 2.5mg/ml; SAL, saline.

other limb: both phenomena have been described in amputees [12,13].

The aims of our work were to determine the extent to which the presence of areas of myofascial hyperalgesia could mirror phantom pain localization and to determine whether their infiltration with an anaesthetic could relieve both myofascial hyperalgesia to static mechanical stimulation and the phantom pain.

In our small series, the most affected parts in the healthy limb were the proximal lateromedial part of the thigh and the anterior compartment (tibialis anterior) in the calf, whereas the areas of major phantom pain representation were essentially related to the foot and ankle. This is in agreement with the clinical data presented in the literature on the prevalent distribution of the phantom and phantom pain to distal areas of limbs [32]. Thus, the presence of myofascial hyperalgesic areas in the healthy limb and their distribution did not seem to exactly mirror the phantom pain areas.

However, notwithstanding this substantial mismatch between phantom pain localization and the presence of myofascial hyperalgesic areas, their treatment was able to reduce the phantom pain in all patients and induce modification in the phantom perception in six of them. It is worth to mention the fact that, as described previously by others [33], saline was also able to partially reduce pain but did not affect the phantom except in a case in which a transient telescopic sensation was reported.

As expected, the anaesthetic injection into the myofascial hyperalgesic areas in the healthy limb completely relieved the pain.

#### **Possible mechanism of phantom pain relief**

The mechanism by which contralateral injection of anaesthetic is able to influence (reduce) phantom pain has not yet been established because until now the real nature of the phantom pain has not been clearly illustrated. A possible pragmatic approach could also take into account other physical modalities applied contralaterally in these patients to find out possible similarities of mechanism of action that can be used as a model of understanding.

Only few contralateral physical treatments are described in the literature. They are TENS [7,9,14] and contralateral local anaesthetic injections [16,17]. All of them have been reported to be highly effective.

TENS has been used by applying high-frequency/low-intensity currents. Its efficacy has been assumed

to be related to a gating mechanism and theoretically limited to segmental short-lasting effects [34]. This view has been recently enlarged (expanded) by the observation of bilateral changes in thermal threshold induced by unilateral application of high-frequency TENS (100 Hz) in a group of healthy individuals and related these changes to a central segmental mechanism of TENS [35,36]. The fact that thermal sensations are carried by fibres histologically similar to pain fibres carrying nociceptive information (namely A-delta and C fibres) can give some support to the theory of contralateral antinociceptive effect of TENS. This hypothesis has also supported the use of electrical stimulation in the clinical battlefield either ipsilateral or contralateral to the amputation, with some success.

Traditional, as well as western, acupuncture, has been encountered into the so-called counter-irritative therapies [37] exerting their analgesic effects by means of hyperstimulations [38]. Its efficacy is related to the activation of antinociceptive systems such as endorphins [11]. Therefore, from a therapeutical point of view acupuncture or electroacupuncture acting on opiate systems can be accounted for inducing a decrease in pain and phantom pain sensation even when contralaterally applied to the painful site [9–11].

The use of anaesthetics differs from the above-mentioned mechanisms (i.e. the spinal gating and the opiate systems) as it is mainly based on the inhibition of afferent inputs at the site of origin, or on the blockade of nociceptive fibres along a peripheral nerve [8]. A possible systemic effect of bupivacaine does not seem to be sustained, as the phantom pain completely disappeared in patient VII in whom only few muscle hyperpathic areas were found and a few millilitres of bupivacaine were used. Moreover, the recorded effect was too fast to be mediated by a systemic diffusion of the drug.

The blockade of afferent inputs, especially if pathological, and the consequent reduction of abnormal sensory barrages to the spinal cord could be taken into account to justify its action. Phantom pain, however, is not influenced by a peripheral blockade and it often persists even after dorsal rhizotomy [39].

Another intriguing hypothesis is that the phantom and the phantom pain are sustained by a dramatic lack of inputs from the amputated limb. A variation of this is that the lack of inputs should be time locked with the huge surge of sensory inputs due to the amputation. In these cases the systemic blockade of all hyperalgesic contralateral areas should theoretically increase the pain rather than reduce it, as seen after lumbar plexus blockade [40]. Moreover, in the light of that, a 'normal

phantom' is usually felt after local anaesthetic blockade of a peripheral nerve [41]. All these do not help in understanding how a contralateral blockade can influence the phantom pain.

A possible explanation of the efficacy of the blockade of sensory and nociceptive inputs to the spinal cord contralaterally to the phantom is the positive sensory phenomenon, called *synchiria* [13], seen in a clinic, in which a cutaneous stimulus that is applied to one limb evokes sensation simultaneously in both limbs. This phenomenon, as well as referred sensations, has been described following stroke, complex regional pain syndrome, and in amputees with phantom limb pain [42].

In *dysynchiria*, touch to the asymptomatic limb evokes the sensation of touch in that limb and pain and *dysaesthesia* on the affected limb [43]. Neither *synchiria* nor *dysynchiria* has been reported in healthy individuals or in patients with minor nerve damage such as acute localized or radicular pain [43]. The mechanisms underlying *synchiria* and *dysynchiria* are the positive aspects we observed and used in our study as using anaesthetic: a blockade of muscle hyperpathic areas in the healthy side (i.e. a reduction of inputs) is able to influence the phantom sensation and painful phantom on the contralateral side. The mechanisms underlined these effects both the positive, *synchiria*, and the negative, the reduction of phantom and pain sensation, could include any of the followings working alone or in combination:

- (1) Changes in spinal dorsal horn function including central sensitization [44], bilateral sensory interneurons or ganglia [45], spinal cord or brainstem commissural interneurons [18], or glial cell activation [46,47].
- (2) Changes in subcortical structures, including changes in thalamic function [19,48], associative somatosensory cortices, the insula, frontal cortices or the anterior cingulate cortex [49–53].

Most of the recent studies are focused on the changes recorded at suprasegmental cortical level following the original idea of a distortion of the *neuromatrix* [54–56]. However, the concept of a *'neuromatrix'* for pain processing has scanty evidence for any particular regional or circuit dysfunction during clinical pain [57].

At the spinal level, many data support a mutual connectivity between the two sides of the cord. For instance, the neurochemical modulation of one side provokes rapid responsivity changes on the corresponding contralateral side [58,59]. In pathological models of peripheral neuropathy, the centrally induced

sensitization of dorsal horn neurons facilitates heterolateral inputs. Sensitization would allow for direct responses of ipsilateral wide dynamic range neurons, accounting for lowered threshold to contralateral stimulations [60]. Neurodynamic events such as sensitization and lowered threshold values are the final outcome of many metabolic and neurochemical events modifying often permanently the responsive features of sensory neurons and driving to the lowered discharge and stimulus thresholds. On the basis of a delicate AMPA and NMDA receptor interaction, sensitization shares many markers with widespread phenomena in the CNS, such as long-term potentiation and memory storages [61,62]. Bilateral input weighing is functionally operative even at higher supraspinal levels. For instance, early reports have already provided evidence on mutual connections in rat somatosensory thalamus [63], as well as on instances of cortical transcallosal connections in humans [64]. This evidence would come along with those fast responses we observed in our patients.

Bilaterality is a far diffused phenomenon both in the sensory and in the motor compartments. For instance, as it has been shown in rats with a peripheral neuropathy, the stimulation of the uninjured paw promoted evoked potentials in the ventral root on the injured side [65].

The dynamic properties induced by the bilateral sensorimotor image of lateralized inputs seem the heritage of strong developmental anatomic design where robust bilateral interactions between the developing neural systems on each side are important for achieving connectivity balance between the two sides of the neuraxis [66].

The fast relief of pain in the patient, as shown in our data, even with few numbers of patients, would match with the speed of signal transition due to paucisynaptic connections between the two sides of the system. These characteristics would explain many of the data here and elsewhere reported, even if obvious pending problems remain – for instance, the strength, the distribution level of the mutual connections and the very role they would play on the clinical stage.

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## Conclusion

Contralateral injections of 1 ml 0.25% bupivacaine in myofascial hyperalgesic areas attenuated phantom limb pain and affected phantom limb sensation. Our study gives a basis of a new method of management of that kind of severe pain to improve the method of rehabilitation of amputee. However, further longitudinal studies with larger number of patients are needed to confirm our study.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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