Inconclusive evidence to support the use of minimally-invasive radiofrequency denervation against chronic low back pain

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Low back pain (LBP), defined as the localized pain or discomfort between the costal margins and superior gluteal line, with or without associated lower limb pain, is one of the most commonly encountered pain syndromes in adults. It is considered chronic LBP (CLBP), when pain persists for more than three months (1). CLBP might be disabling with increased missing hours of productive work or of personal activities and it can also be associated with significant excess of healthcare costs (2). Commonly, CLBP also gives rise to the genesis or exacerbation of various psychiatric disorders, such as depression and/or anxiety (3).

Its clinical phenotype greatly varies depending on the underlying pathophysiology of the condition. On clinical grounds, CLBP can be categorized as this pain syndrome that (I) is associated with a specific underlying disease; (II) has prevalent the neuropathic component and; (III) is of mechanical origin being non-specific or without recognisable cause in the majority of cases. However, due to the complexity and heterogeneity of the condition, the diagnostic approach can be problematic, before the physician eventually is able to decide on the pathophysiology and source of CLBP origin (4). Besides this, there is currently lack of consensus regarding an objective measure or specific diagnostic criteria to accurately monitor its incidence and severity (5).

CLBP often comprises both nociceptive and neuropathic components. It is urged that both of these components should be recognized and thoroughly treated separately in order to achieve a meaningful response to oral pharmacotherapies. However, clinical experience shows that the neuropathic component of CLBP, being the result of an underlying somatosensory lesion, remains often underdiagnosed and thus undertreated (5). The main reason to account for the latter fact is that patients who do not have the typical radicular presentation are often misdiagnosed as only having the nociceptive component of LBP. Recently it was demonstrated that appropriately use of behavioural evaluation and sensory examination led to successful differentiation between the nociceptive and neuropathic components in CLBP (6).

On the other hand, if the neuropathic component of LBP is successfully recognized, the use of neuropathic pain medications with antidepressants to target the serotonin-noradrenaline system, e.g., duloxetine and/or antiepileptic drugs, e.g., gabapentin or pregabalin is often hampered by lack of clinically meaningful analgesia, by evidence of refractoriness or increased risk of adverse effects. Drug to drug interactions might also occur when combining oral pharmacological agents to target both the nociceptive and neuropathic components of CLBP (3). As such, its pharmacological therapy still remains an unmet need in clinical practice and further study is needed to identify a proper sensory phenotyping of CLBP patients to allow the development of more targeted therapies (3,7).

Taking into account the modest efficacy of systemic treatments and that CLBP is generated from the lumbar spine or its supporting structures, there is an increasing use over the last years of minimal invasive techniques to alleviate LBP, providing that the pain originates from single sources, including facet joint, disc, sacroiliac joint or a combination of these (8). There is evidence from uncontrolled trials that radiofrequency denervation is effective against CLBP, when strict selection criteria are adhered to establish the diagnosis and a specific procedure is applied (9,10). However, a recently published Cochrane review of 23 randomized clinical trials contradicts the latter findings, as it concludes for a modest effect of radiofrequency denervation on facet joint pain, mainly as a result of poor quality evidence of the studied procedures. Authors urged the need for high-quality RCTs with larger study samples to obtain enough statistical power, before one can with confidence conclude on the significance of radiofrequency denervation against CLBP (11). Moreover, the inconsistency in the improvement of sacroiliac and facet joint pain over time, as well as the absence of neurologic adverse events create relevant questions about if there is any robust pathophysiologic mechanism by which this intervention is acting. To be more specific: (I) why the effect of neurolysis is not sustained over time and; (II) why the injury of a nerve to block the transmission is not associated with significant rates of local neurological adverse events?

We read with great interest the recently published study by Juch *et al.* (12), in which authors presented the outcome of three pragmatic multicenter, nonblinded randomized clinical trials on the effectiveness of minimal interventional treatments in Dutch participants with CLBP. These studies, coined as the "The Mint Randomized Clinical Trials" were conducted to provide evidence of higher quality on the topic by overcoming the limitations of previous publications as these were delineated in the Cochrane review (11). To achieve that objective, authors delivered radiofrequency denervation, added to a standardized exercise program (intervention arm) *vs.* physiotherapy alone (control arm) on an adequate number of unresponsive to conservative care CLBP patients. Participants had a single positive diagnostic block at the facet joints (n=251 participants), sacroiliac joints (n=228 participants), or a combination of facet joints, sacroiliac joints, or intervertebral disks (n=202 participants). It was required per protocol a decrease of at least two points in the numeric pain scale (NPS; range, 0–10) measured three months after the once-delivered intervention to score for meaningful clinical analgesia. The mean baseline pain intensity of participants was 7.1, according to NPS. A total of 344 patients was allocated to the intervention arm and 337 were used to serve as controls. The demographics were comparable between arms, whereas the majority of participants (n=599; 88%) completed the study, being able to present in the predetermined 3-month after procedure follow up visit. Only the long-term follow-up of the sacroiliac trial can be assumed as underpowered due to the significant number of patients lost, mainly in the non-interventional arm. Notably, the combined trial has almost 30% of patients who failed to complete the exercise treatment in the non-interventional arm. Nevertheless, the analysis of data all together highlighted an insignificant mean difference in pain intensity between the radiofrequency denervation and control groups at 3 months, independently if the procedure was delivered in the facet joints, sacroiliac joints or combined. Taking into account the several limitations in their work, including among others the unblinded study design; the absence of placebo; the lack of reference standard for diagnosing facet or sacroiliac joint pain as well as the lack of correctional adjustments for multiple comparisons, the authors provided evidence for a low efficacy of radiofrequency denervation in CBLP patients, thus advising against its use (12). Normally, the applied nonblinded study design would have been against the treatment arm if the intervention was really effective; but in the current case, one can claim that it only reinforces the results of this negative study. Likewise, considering that placebo can improve up to 30% of pain perception, the lack of sham or fake radiofrequencies use as a placebo intervention in the current setting (12) further reinforces, in our opinion, the negative results.

Several questions arose from the results reported by Juch *et al.* (12); the majority of those have been openly expressed in three letters to the editor (13) sent by other groups to criticize numerous methodological aspects of the "Mint Trials". The main facets of criticism included: (I) authors employed less stringent diagnostic criteria to select patients for delivering radiofrequency denervation, compared to the Spine Intervention Society guidelines. This was deemed inappropriate as it may confine significant bias resulting in high false-positive rates (25–45%) of CLBP diagnosis (14). Juch *et al.* (12), acknowledged the significance of this issue and proceeded to online corrections of references (13), although it is difficult for us to comprehend the real meaning of this action, because references might have been changed but the definition used as a diagnostic criterion is impossible to correct at a second

stage and thus remained the same; (II) it was also claimed that the use of a small gauge diameter electrode decreased the possibility of adequate neurolysis, thus resulting in significant technical bias underpinning the likelihood of false-negative outcome after the intervention. Juch *et al.* (12), acknowledged that the needle size, its placement and other procedure's parameters might vary in different countries and settings where the procedure is performed with the much larger 18-gauge diameter electrodes. However, as they state, the use in their setting of a small gauge diameter electrode (22G) was in keeping with the national Dutch standards and was also evidence-based; (III) the use of mean pain intensity, graded by a numeric rating scale, as the primary endpoint was also disputed and was suggested that the latter together with the definition of procedure's efficacy at the low value of 30% reduction of pain, might have also been potent factors enhancing bias. Juch *et al.* (12), proved with the use of post-hoc analyses that there was no evidence of bias from the method they applied.

Finally, the most important criticism was probably about the applied method to diagnose facet pain with the use of single and not double positive diagnostic facet medial branch block prior to radiofrequency denervation. As acknowledged by the authors (12), to apply a single block could indeed result in lower diagnostic specificity and increased false-positive rates, but this approach was in keeping with national Dutch practice and the threshold of pain reduction of at least 50% (positive response) after a single block is most commonly applied for research purposes. However, one cannot disregard that the false-positive diagnostic rate of performing single rather than double blocks can be up to 45% (15).

Nevertheless, in our opinion the study by Juch *et al.* (12) is of significance, because it is presenting for the first time the summary outcome of three randomized controlled, sufficiently powered, in pragmatic conditions, trials, on the efficacy of radiofrequency denervation to alleviate CLBP. This study clearly concluded negatively on the clinically meaningful analgesia of the intervention.

However, taking into account the above-mentioned constructive debate on the topic, as also recent controversial evidence from other groups demonstrating a significant and long-lasting pain relief after delivering radiofrequency denervation in appropriately selected patients (16), further studies with improved study design and procedures, than that applied by Juch *et al.* (12), are warranted. Bearing the current evidence in mind, there is an obvious need of future studies to overcome all the current methodological limitations so as to eventually shed light on the real analgesic effect of minimally-invasive radiofrequency denervation among patients with CLBP.

As a closing remark, we can say that CLBP possess a quite generic definition, including many different causes and mechanisms. As such, it is necessary to establish its better definition beyond topographical regions, and a more analytic delimitation of the underlying causes to improve the therapeutic approaches. We would also like to encourage search for any objective neurophysiological measure to avoid the present controversy on the topic. Towards this view, further studies applying quantitative sensory testing of C fibers in corresponding spinal dermatomes or technically adapted microneurography recordings from CLBP patients, are warranted to test if there is any real neurophysiological background to recommend this intervention. Finally, researchers on the topic should reach to a consensus regarding the diagnostic criteria that are to be used in future studies. Given the current lack of effective pharmacological analgesics to treat this commonly encountered pain syndrome, the dispel of any doubts on this specific topic is very important on clinical grounds.

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Footnote

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