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Fluoroscopy-guided high-intensity focused ultrasound neurotomy of the lumbar zygapophyseal joints: a prospective, open-label study

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ABSTRACT

Objective The objective of this study is to investigate safety and effectiveness of a fluoroscopy-guided high-intensity focused ultrasound (HIFU) system for thermal ablation of the lumbar medial branch nerves.

Methods This dual center prospective cohort study enrolled 30 participants with lumbar zygapophyseal joint syndrome. Each participant previously had a positive response to either a single diagnostic analgesic block or radiofrequency ablation (RFA). The primary effectiveness outcome was individual responder rate, defined as a reduction of two points or more on the pain intensity numerical rating scale without an increase in opioid intake, or a reduction in opioid intake without an increase in pain at 6 months after the intervention. The primary safety outcome was procedure-related or device-related adverse events (AEs). Secondary outcome variables included MRI evidence of tissue ablation, Oswestry Disability Index, 12-Item Short Form Health Survey, Brief Pain Inventory, and Patient Global Impression of Change.

Results The individual responder rate was 89.7% at 2 days, 89.7% at 7 days, 72.4% at 14 days, 82.1% at 30 days, 59.3% at 90 days and 82.6% at 180 days. The average Numeric Rating Scale for pain severity decreased from 7.1 at baseline to 3.0 (N=29) after 2 days, 3.0 (N=29) after 7 days, 3.1 (N=29) after 14 days, 3.2 (N=28) after 30 days, 4.3 (N=27) after 90 days, and 3.3 (N=23) after 180 days. All participants tolerated the procedure well with no significant side effects or complications.

Conclusions Fluoroscopy-guided HIFU neurotomy achieved clinical responses comparable with RFA, and there were no significant device-related or procedure-related AEs.

Trial registration number NCT04129034.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Initial preclinical and clinical evidence have confirmed the safety and preliminary effectiveness of using fluoroscopy-guided high-intensity focused ultrasound (HIFU) as a thermal neurotomy method of the lumbar medial branch nerves.

WHAT THIS STUDY ADDS

⇒ The current study adds further clinical and imaging evidence based on a pragmatic, real-life study design and conservative outcome goals.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study strengthens the position of fluoroscopy-guided HIFU neurotomy of the lumbar medial branches as a safe, effective, and non-invasive method to alleviate low back pain.

INTRODUCTION

Lumbar zygapophyseal joint (z-joint) syndrome is a common diagnosis among patients with chronic low back pain.[1–4] Routine standard-of-care interventions to manage pain associated with z-joint syndrome include blockade of the medial branches of the z-joint nerves or blockade of the joint itself, often followed by radiofrequency ablation (RFA). Some studies have concluded that RFA is ineffective[5–7] while others report significantly positive results.[8–12] Patient selection, anatomical precision, and lesion size are cited as determinants of success for treating z-joint syndrome with RFA.[13–15] Despite its widespread clinical adoption, the main drawback of RFA is its invasiveness, which can cause periprocedural and postprocedural pain, bleeding, and spinal cord and nerve root damage.[16]

We previously conducted a pilot clinical trial with 10 participants to test a novel, non-invasive method for treating z-joint syndrome using high-intensity focused ultrasound (HIFU) and reported similar effectiveness as RFA and no adverse events (AEs).[17] The current clinical trial was designed as a larger, open-label, prospective clinical trial to provide further evidence for the efficacy of fluoroscopy-guided HIFU neurotomy of the lumbar medial branch nerves.

METHODS

The study was registered on ClinicalTrials.gov (NCT04129034, September 24, 2019). 30 participants with z-joint syndrome were recruited between September 2019 and October 2022 at two enrolment sites (figure 1). The first patient was recruited on November 11, 2019. The COVID-19 pandemic led to a slower than planned recruitment. The investigational device (figure 2) was a 1-MHz

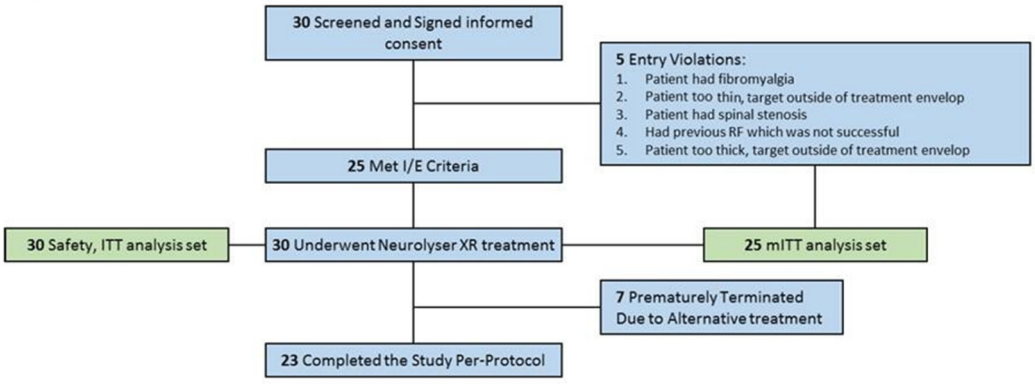

Figure 1 Study enrolment flow chart. ITT, intention to treat; mITT, modified ITT.

fluoroscopy-guided HIFU system (Neurolyser XR, FUSMobile, Alpharetta, Georgia, USA).

Inclusion and exclusion criteria

Patients older than 50 years with bilateral or unilateral z-joint syndrome lasting more than 6 months were eligible to enter the study. Eligibility was based on a clinical picture of axial low back pain alleviated by recumbency and documented positive response (greater than 70% pain relief) to a previous single lumbar medial branch block within the past 12 months and/or a positive response (greater than 70% pain relief) lasting more than 6 months after the most recent z-joint RFA. All participants reported a 6 or higher average pain on a 11-point Numeric Rating Scale (NRS 0–10) within 30 days before the study procedure. See online supplemental material for inclusion and exclusion criteria.

All participants signed informed consent.

Outcome assessments

Individual responder was defined as either (1) a reduction by two points or more on the NRS without an increase in the opioid intake or (2) a reduction of opioid intake without an increase in pain at 6 months after the intervention. FDA recommendations concerning the future randomized controlled clinical study outcome goals were followed.

All periprocedural AEs were captured and categorized by the treating physician. If a participant reported an AE, the treating physician rated it as mild, moderate, or severe and noted its relation to the procedure and/or device.

Figure 2 The FUSMobile, Neurolyser XR, 1-MHz fluoroscopy-guided HIFU device. HIFU, high-intensity focused ultrasound.

The following questionnaires were used to measure effectiveness: average 24-hour 11-point NRS, the Oswestry Disability Index (ODI), 12-Item Short Form Health Survey (SF-12), Brief Pain Inventory SF (BPI-SF), and the Patient Global Impression of Change (PGIC). Investigators also collected data on opioid consumption, fluoroscopy time, and focused neurological examinations. Optional postprocedure MRI was used to evaluate lesion size and location. Follow-up appointments were performed via telephone interviews or office visits (online supplemental materials).

HIFU procedure

Participants were instructed to take their regular analgesics up to 1 hour before the procedure, avoid applying oily lotion or cream for 24 hours prior to treatment, and fast for 8 hours before treatment. All opioids taken within 24 hours and sedative medications given during the procedure were recorded. Participants remained awake and communicated with the treatment team throughout the procedure.

Procedures were performed by an interventional pain physician experienced in lumbar RFA with the help of a radiology technician in an interventional pain suite with mobile C-arm fluoroscopy guidance (GE OEC 9900 Boston, Massachusetts, USA, or Siemens Siremobil Compact L, Munich, Germany). The team used a coupling gel pad (FUSMobile) to optimize transducer focal depth position pertinent to body habitus.

Participants were placed prone on the procedure table, and a positional prop was placed under the abdomen to mitigate lumbar lordosis and improve acoustic coupling. Hair or oily residues were removed if needed, and skin was evaluated for extensive scarring or lesions.

HIFU energy was delivered with the Neurolyser XR annular-array transducer, which converges multiple ultrasound beams in an incoherent mode[18] onto a target location. Each beam passes through tissue with little effect, but at the focal point where the beams converge, a significant increase of acoustic intensity is achieved.[19] Overlapping the acoustic focal spot with the bone-tissue interface leverages the high acoustic absorption of bone to create predictable thermal ablation at the bone-tissue interface.

The Neurolyser XR imaging workstation analyzes fluoroscopy images in real time and provides real-time targeting overlay. Compared with the pilot study,[17] the Neurolyser XR system used in this study had improved targeting accuracy and speed due to the integration of an optical camera, and image-processing and spatial positioning software modules.

The sonication target at the junction of the transverse process and the superior articular process was chosen based on a published cadaveric study that recommended a slightly more distal ablation of the medial branch nerve.[20] This location allows less oblique fluoroscopy angulation as compared with RFA and provides more selective ablation of the articular twigs, sparing the lateral branches and possibly preserving muscular innervation.

Before the start of the procedure, the participant was instructed to press the handheld stop sonication button if experienced severe back pain or any pain below the knee, or motor stimulation occured during energy delivery. If a participant pushed the stop button during the verification or ablation sonication, the sonication was aborted immediately. The treating physician then examined the participant and decided whether to adjust targeting before resuming sonication. The physician could also stop the sonication if indicated.

To verify expected tissue changes, participants were offered an optional contrast-enhanced MRI examination within 5 days postprocedure. Sagittal T2w, axial T2w FATSAT, T1w with and without FATSAT, and T1w FATSAT post-contrast views were obtained. A set of subtraction axial images was created based on the T1w FATSAT with and without contrast. The MRIs were reviewed for edema (increased T2 signal) and ablation (necrosis surrounded by ring enhancement).

Participants were followed-up at clinics and/or via telephone appointments with research assistants on post procedure days 2, 7, 14, 30, 90, and 180 to rate their pain intensity, report side effects, and complete secondary outcome questionnaires. Any complaints potentially related to thermal damage of the skin or exiting nerves prompted a visit with the physician. Participants were allowed to exit the study at any time and were offered RFA as a rescue treatment.

Study oversight

Data were independently monitored by the Centre for Innovative Medicine (McGill University, Montreal, Quebec, Canada) and reported to Health Canada as required. During the study, the protocol follow-up period was shortened to 6 months from the original 12 months, and an option for a telephone visit replaced an office visit for participants without any neurological symptoms during COVID-19 restrictions. The IRB and Health Canada approved all protocol changes.

Statistical analysis

Statistical analysis was descriptive and included safety data, primary and secondary effectiveness, and radiological outcomes. Participants who withdrew from the study were excluded from further data analysis and were considered as treatment failures in the treatment success ratio analysis.

Numerical variables were tabulated using mean, SD, minimum, median, maximum, and number of observations. Categorical variables were tabulated using number of observations and percentages.

An additional modified intention-to-treat (mITT) analysis was performed on the same data set to exclude five participants who were erroneously enrolled despite failing to satisfy the inclusion/exclusion criteria. Primary efficacy analyses were based on the number of responders.

The hypothesis tested was that of a 50% responder rate. This hypothesis was tested by constructing a 95% Clopper-Pearson CI. If the lower limit of the CI was greater than 50%, the null hypothesis was rejected, and the study was deemed successful.

Secondary efficacy analyses of the two data sets were conducted on:

- Frequency distribution of PGIC scores.
- Descriptive statistics of raw change in NRS.
- Descriptive statistics of the BPI-SF, NRS, ODI, and SF-12 questionnaire scores.

Table 2 Participants with at least a 2-point reduction in pain by visit (see mITT analysis in online supplemental material)

Follow-up visit (days)	At least a 2-point reduction in pain				Total	
	Yes		No			
	N	%	N	%	N	%
2	26	89.7	3	10.3	29	100.0
7	26	89.7	3	10.3	29	100.0
14	21	72.4	8	27.6	29	100.0
30	23	82.1	5	17.9	28	100.0
90	16	59.3	11	40.7	27	100.0
180	19	82.6	4	17.4	23	100.0

mITT, modified intention to treat.

RESULTS

Of the 30 participants, 16 (53.3%) were male and 14 (46.7%) were female. The mean participant age was 67.1 years (52, 83), and the average body mass index was 28.4 kg/m^2 (19.5, 46) (online supplemental materials). Seven of the 30 participants exited the study before the 6-month follow-up visit. 19 of 150 follow-up visits occurred slightly outside the scheduled window due to COVID-19-related issues. Protocol deviations were recorded and reported to the IRB.

Primary outcomes

No device-related or procedure-related severe or serious AEs were reported. The ITT responder rate was 66.7%, with a 95% confidence level of 47.2% to 82.7%. The mITT responder rate was 72.0%, with a 95% confidence level of 50.6% to 87.9% (table 1).

The ITT individual responder rate was 89.7% at 2 days, 89.7% at 7 days, 72.4% at 14 days, 82.1% at 30 days, 59.3% at 90 days, and 82.6% at 180 days (table 2).

The individual responder determination included changes in opioid equivalency levels. Of the 30 participants, 8 were taking opioids at baseline, with an average morphine equivalency of 22.2 mg/day, (3.75, 60.0). Of these eight, three discontinued and did not resume taking opioids by the last study visit; an additional two reduced dosage (one from 30 to 15 mg/day and one from

Table 1 Response rates for the primary efficacy endpoint at the 6-month (180 days) visit

Analysis set	Number of participants	Number of responders	Per cent of responders	Lower 95% CL	Upper 95% CL	One-sided P value	Two-sided p value
ITT	30	20	66.7	47.2	82.7	0.049	0.098
mITT	25	18	72.0	50.6	87.9	0.022	0.043

ITT, intention to treat; mITT, modified ITT.

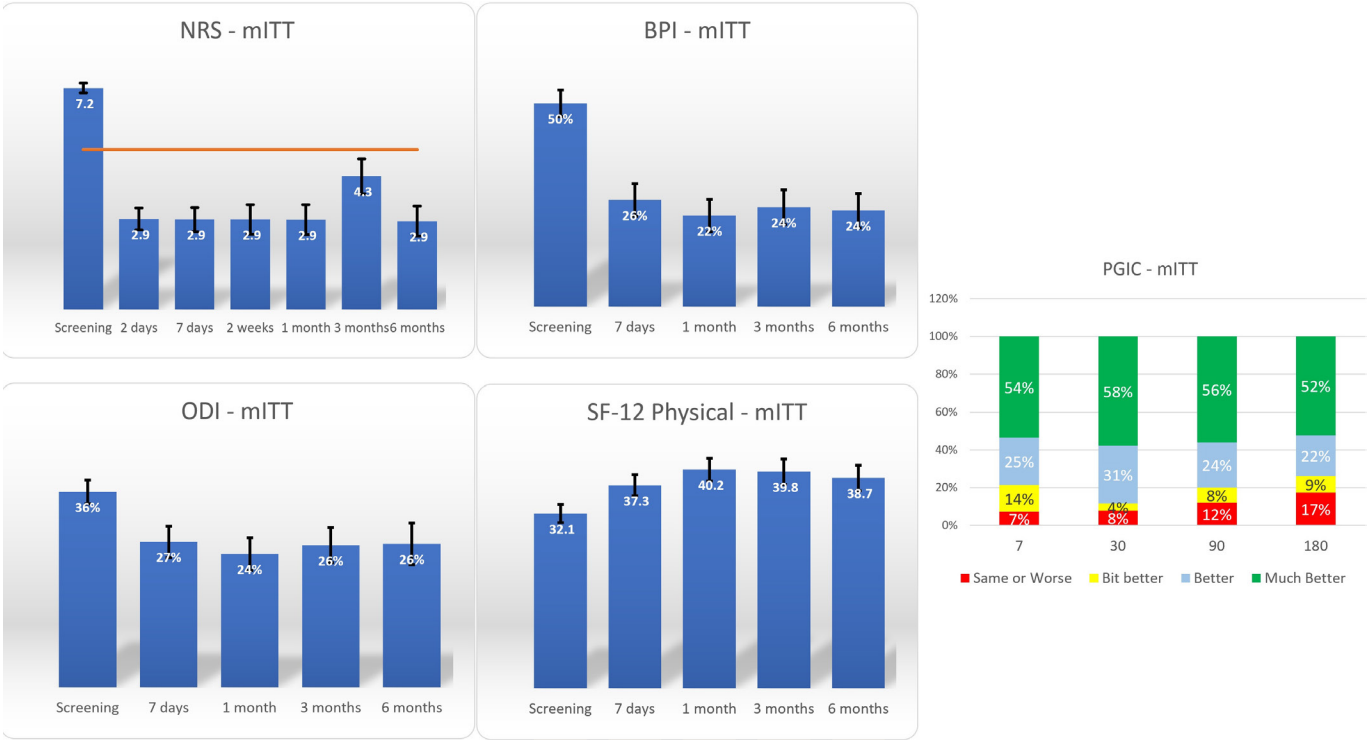

Figure 3 Graphical representations of participants' effectiveness questionnaires over 6 months. BPI, Brief Pain Inventory; mITT, modified intention to treat; NRS, Numeric Rating Scale; ODI, Oswestry Disability Index; SF-12, 2-Item Short Form Health Survey.

60 to 7.5 mg/day). One participant maintained opioid dose, but their 6-month NRS score decreased from 7 to 2. The remaining two participants dropped out, but one of them reduced dosage from 22.5 to 15 mg/day at 3 months (with their NRS initially decreasing from eight at baseline down to four and then back up to 7.5 at 3 months); the other maintained their opioid level but their NRS decreased from 7 to 3.5 at the 2-week visit. None of the participants increased their opioid dosage.

Secondary outcomes

At 6 months, mITT BPI pain interference decreased from 50% to 24% and disability impact (ODI) decreased from 36% to 26%. SF-12 physical scores improved from 32.1 to 38.7. PGIC showed 52% of participants reporting a "much better" at 6 months and another 22% reporting "better" results for a total of 74% (figure 3).

Of the 15 participants who consented to undergo postprocedure MRI scans, 2 scans were excluded because of MRI research protocol violations. The 13 remaining MRI studies were analyzed by a neuroradiologist (SL) who was blinded to all clinical and procedural data. One of the 13 MRIs was done without contrast; therefore, that scan was evaluated for edema only. At the target location, tissue edema, manifested by increased T2 signal, was detected in 67% (55/82) of the target locations. Ablation-induced necrosis, evidenced by a central non-enhancing region surrounded by enhancement, was found at 55% (42/76) of the target locations (see online supplemental materials).

Nine of 13 participants had edema in more than 50% of targeted locations, and the responder rate for this group was 78% (7/9). The remaining 4 of 13 participants, who had edema in less than 50% of target locations had a responder rate of 50% (2/4).

Seven of 12 participants had an ablation in more than 50% of target locations. The responder rate in this group was 86% (6/7). The other 5 of 12 participants with an ablation in less than 50% of target locations had a responder rate of 40% (2/5).

The average procedure time was 41.5±20.4 min, with an average of 5.6 (1–8) ablations per participant. The average periprocedural pain rating was 5.2 (0–9), which was reduced to 2.4 (0–6) within 30 min after the procedure. The average duration of fluoroscopy exposure was 41.6 sec (16.0–79.5), and the average number of fluoroscopy images was 64.4 (24–176). Technical proficiency improved over time (see online supplemental materials).

DISCUSSION

The current study confirmed that fluoroscopy-guided HIFU neurotomy can be safely performed with the Neurolyser XR device (with its system upgrades for improved targeting). No significant AEs occurred during the procedure or within the 6-month follow-up period. Postprocedure clinical neurological examinations, when they were indicated due to subjective complaints, revealed no abnormal findings. There were no interruptions to the procedure due to a safety event, although one procedure was aborted when the target was deemed too superficial, outside the treatment envelope.

The use of HIFU for managing z-joint chronic pain is not a new concept. MR-guided focused ultrasound (MRgFUS) for the treatment of z-joint syndrome has obtained a CE mark.[21] However, clinical adoption has been challenging, likely due to a high cost and the cumbersome and lengthy procedural routine associated with the MRI. To date, only two small clinical studies have investigated HIFU as an ablation method in palliation of z-joint syndrome. In the Weeks *et al* report, 18 patients underwent MRgFUS treatments.[21] The average procedure time was 188 min, and 10 patients received sedation during the procedure. There were no reported AEs. At 6 months, 13 patients reported a reduction in average NRS to 3.87 from a pretreatment of 6.42

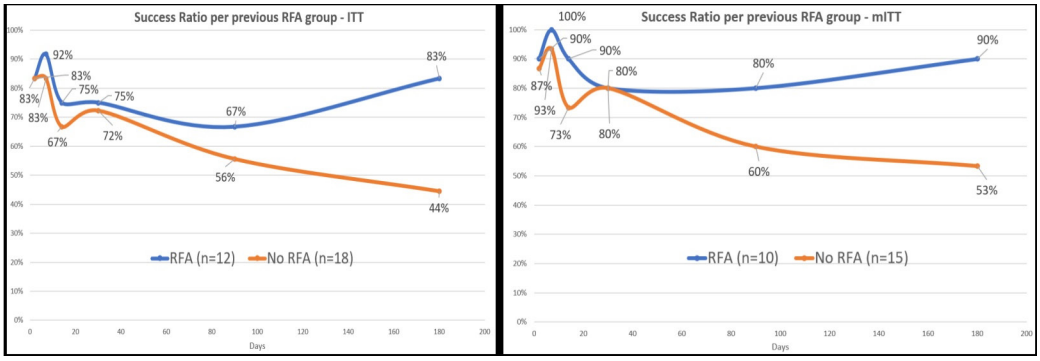

Figure 4 Graphical representations of participants' success ratio per previous RFA experience. mITT, modified intention to treat; RFA, radiofrequency ablation.

(60.2%). This was accompanied by a 45.8% improvement in the ODI and a 61.9% reduction in the BPI interference score. A second, more recent study also used MRgFUS interventions.[22] Of 21 treatments with clinical follow-up of at least 3 months, 12 (57.1%) had more than 3 months of pain relief, 2 (10%) had less than 3 months of benefit, 6 (30%) reported no benefit, and 1 (5%) patient was lost to follow-up. Notably, in patients who reported at least some benefit with prior conventional RFA, 8 of 10 (80%) benefited from the MRgFUS procedure, whereas only 14.3% of patients without any response to RFA benefited. The authors speculated that some patients did responded to RFA because of technical challenges with MRgFUS. The results of these two studies were modest but comparable with our work and RFA outcomes. However, these two previous studies implemented a completely different approach. Not only MRI guidance was used, but also the posterior joint capsule itself was targeted. Which of these two potential targets is more promising to achieve lumbar z-joint denervation remains undetermined.

We hypothesized that a HIFU device that used fluoroscopy guidance (similar to RFA) would have potential advantages by eliminating the invasiveness of RFA, lowering procedural costs and postprocedure pain, and reducing procedural time. Although individuals with bleeding disorders were excluded, the physical properties of HIFU allow its use in patients receiving antiaggregant and anticoagulants. The same tenet is applicable for those with implanted cardioverters and previous lumbar instrumentation.[23 24]

Elimination of aseptic preparations and reduction of radiation exposure should also be considered potential advantages over RFA.[16]

Before embarking on this project, we reviewed imaging predictors from archived, anonymized CT data[25] and conducted acoustic simulation[18] and preclinical studies.[26 27] Lastly, we performed and published the 10-participant pilot study.[17] A constructive critique of the pilot study was considered and used to improve the methodology and processes of this study.[28] In the current trial, the HIFU procedure was well tolerated. Only two participants requested and received minimal intravenous conscious sedation. Pain scores during sonication were rated as "mild to moderate" and decreased to "none to mild" within 30 min of the procedure (online supplemental materials). None of the participants complained of procedure-related pain before discharge.

The results at 6 months were comparable with those reported in optimistic RFA studies.[8 16 29] However, the onset of pain reduction after HIFU was rapid, with clinical efficacy observed as early as on day two. An instance which is uncommon after RFA. Protracted post-RFA pain is a well-known clinical observation, although its duration and severity have not been highlighted in literature.

Overall, seven participants left the study before the 6-month follow-up visit, including two due to the protocol violations. In the one case, the target was outside of the treatment envelope (too superficial), and another participant did not meet the inclusion criteria as it was later discovered his previous RFA had failed. Five participants exited the study due to dissatisfaction, although three of the five were considered responders (eg, pain diminished, opioid dose decreased, both NRS and opioid decreased). The dissatisfaction claim is subjective and may have been related to unreasonable expectations. The participants with high expectations who elected to leave the study and resort to alternative treatments, including RFA, did not achieve the desired absolute reduction of their pain regardless of the subsequent interventions.

Other secondary outcome variables, including ODI, SF-12, BPI-SF, and PGIC, demonstrated positive trends in both the ITT and mITT groups. Although the study was not powered to show statistical significance of the secondary outcomes, average improvement in SF-12, BPI, and PGIC reached and surpassed minimal clinically important difference (MCID).[30 31] The ODI improvement of 9.1 points did not reach MCID[32]; however, the mean ODI before the procedure was only 35.9 ("moderate disability"). Therefore, it is not surprising that with limited sample size, the magnitude of change was relatively small.

The observed phenomenon of increased pain score on NRS at 3 months followed the same pattern as in the previously published pilot study.[17] In the pilot study discussion, we speculated that it could be related to small sample size or a diminished expectation-related benefit. However, even with a larger group, the observed pattern remained mainly unanswered. It may be partially related to the fact that the largest number of participants left the study at 3 months (34.8%), resulting in the total higher NRS score at 3 months. It may also be related to stopping or reducing over-the-counter and opioid medications, increased activity level, or other undetermined factors. When grouping participants per previous RFA experience, the group with no previous RFA demonstrated more failures (figure 4). Also, participants who had a previously beneficial RFA completed the study with a success ratio of 83% (ITT) and 90% (mITT) at 6 months. The participants who were enrolled based on clinical picture, age, and a positive diagnostic block responded with a success ratio of 44% (ITT) and 53% (mITT). The same observation is valid in case of repeat RFA. Those who have had RFA with lasting pain relief are prone to respond to the subsequent

RFAs. Although a reproducible success may have an element of couching or expectation, pain relief lasting more than 3 months is unlikely attributed to placebo response. It should be rather seen as a real gain due to the correct clinical diagnosis of lumbar z-joint pain and effectiveness of RFA for these individuals. Post hoc evidence supported this hypothesis. The non-responders exited the study, and seven participants underwent a rescue RFA procedure. None of these seven participants achieved a clinical benefit following RFA. A recently published MRgUS study reported the same observation.[22] Those who had a positive experience with RFA responded better to the HIFU procedure.

Consensus practice guidelines on interventions for lumbar facet joint pain from a multispecialty, international working group supported the clinical and recommended "lumbar medial branch RFA on recurrence of pain in patients who experience a minimum of 3 months of improvement (and preferably 6 months improvement for multiple procedures)."[16]

Improvements in the material design and software used in this current study afforded superior procedural navigation and targeting, which decreased procedure time and radiation exposure (estimated by fluoroscopy seconds) and made the procedure process more intuitive. We plan to present comparative quantitative data in a future publication to support these claims. The previous study defined the "eye of the scotty dog" as the ablation target site used for a typical medial branch block. This location requires a oblique view of 15°–20° to bypass the base of the superior articular process. During the HIFU procedure, this tilt created technical difficulties in maintaining stable cradle positioning and acoustic coupling. In addition, the oblique view carries the risk of damaging motor twigs and lateral branches, producing inadvertent thermal damage of the lateral process and the joint capsule. In the current study, we used a more distal target for the medial branch nerves.[20]

MRI confirmation of edema or ablation was found in 67% and 55% of the targets, respectively; their presence portends improved clinical response in our data set. In a swine model, Krug *et al*[33] demonstrated consistent visualization of edema on T2 images and central hypoenhancement with surrounding hyperemia on postcontrast images after focused ultrasound of the more distal medial branch nerve along the facet joint. Histology revealed that the paraspinal skeletal muscles, which are prominent in the swine with almost no paraspinal fat, showed a coagulative necrosis that prevented delivery of intravenous contrast to the core of the ablated region. In our preclinical study, the same phenomenon was observed. An equipotent sonication at 1000–1500J resulted in a discrete medial branch necrosis in 71% and 86%, respectively.[27] However, any attempt to correlate between a swine model and clinical MRI would have been grossly speculative. Because this study did not confirm MRI signal changes in all participants, one must consider that the human paraspinal region differs from swine. The elderly, and patients with disuse atrophy from back pain and nerve damage, commonly demonstrate abundant infiltration of the paraspinal musculature with fat, especially adjacent to the bony structures near the medial branch nerves. Compared with skeletal muscle, fat may not manifest areas of coagulative necrosis and edema with similar signal changes; thus, further research with varying MRI parameters within muscle and fat is warranted. Nonetheless, imaging confirmation of HIFU lesions positively associated with the observed response. MRI findings of edema or necrosis (ablation) in more than 50% of targeted locations were linked to 78% and 86% positive response, respectively, whereas when edema or ablation was found in less than 50% of lesion locations, the responder rate was 50% and 40%.

Study limitations

The study limitations include an observational design, exclusion of non-responders from subsequent follow-up visits, and a mixed population of participants who benefited from RFA and those who only had one affirmative diagnostic medial branch block.

The matter of a potential conflict of interest must also be addressed. The majority of the research team are either employees or paid consultants of the study sponsor. This conflict is almost inevitable when conducting premarket research for regulatory approval. To mitigate the conflict of interest, an independent body (the Centre for Innovative Medicine, McGill University, Montreal, QB) rigorously monitored this study, and Health Canada audited one of the two enrolment sites (Toronto Western Hospital). None of the investigators participated in the recruitments, conducted follow-up visits, entered data, or had access to research folders.

CONCLUSIONS

Based on clinical and imaging data, fluoroscopy-guided HIFU ablation-based neurotomy of the lumbar medial branch nerves demonstrated feasibility and promising results for the treatment of lumbar z-joint syndrome. At the very least, the HIFU method appears to be safe and well tolerated.

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Contributors MG is the author acting as guarantor. MG, RA and AH designed the study. MG, KJS, AB and VD performed the study. SL, NR, EM and BS supported technical aspects of the study and analyzed radiological findings and clinical results. The entire team participated in writing and editing the manuscript.

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Competing interests AH and RA are the founders of FUSMobile. MG is the chief medical officer of FUSMobile and holds an option to buy ordinary shares. EM and BS are employees of FUSMobile and hold an option to buy ordinary shares. EM and SL hold shares and ordinary options in FUSMobile.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the study was approved by Health Canada (Investigational Testing Authorization number 302223), the University Health Network Research Ethics Board, and Veritas IRB, serving as the central institutional review board. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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