ORIGINAL CLINICAL RESEARCH REPORT

Smallest Clinically Meaningful Improvement in Amputation-Related Pain and Brief Pain Inventory Scores as Defined by Patient Reports of Global Improvement After Cryoneurolysis: a Retrospective Analysis of a Randomized, Controlled Clinical Trial

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BACKGROUND: The smallest meaningful improvement in pain scores (minimal clinically important difference [MCID]) after an analgesic intervention is essential information when both interpreting published data and designing a clinical trial. However, limited information is available for patients with chronic pain conditions, and what is published is derived from studies involving pharmacologic and psychological interventions. We here calculate these values based on data collected from 144 participants of a previously published multicenter clinical trial investigating the effects of a single treatment with percutaneous cryoneurolysis.

METHODS: In the original trial, we enrolled patients with a lower-limb amputation and established phantom pain. Each received a single-injection femoral and sciatic nerve block with lidocaine and was subsequently randomized to receive either ultrasound-guided percutaneous cryoneurolysis or sham treatment at these same locations. Investigators, participants, and clinical staff were masked to treatment group assignment with the exception of the treating physician performing the cryoneurolysis, who had no subsequent participant interaction. At both baseline and 4 months (primary end point), participants rated their phantom limb pain based on a numeric rating scale (NRS) and their interference of pain on physical and emotional functioning as measured with the Brief Pain Inventory's interference subscale. They subsequently qualitatively defined the change using the 7-point ordinal Patient Global Impression of Change (PGIC). The smallest clinically meaningful improvements in phantom limb pain and Brief Pain Inventory scores were calculated using an anchor-based method based on the PGIC.

RESULTS: The median (interquartile range [IQR]) phantom pain NRS (0–10) improvements at 4 months considered small, medium, and large were 1 [1–1], 3 [3–4], and 4 [3–6], respectively. The median improvements in the Brief Pain Inventory interference subscale (0–70) associated with a small, medium, and large analgesic changes were 16 [6–18], 24 [22–31], and 34 [22–46]. The proportions of patients that experienced PGIC ≥5 were 33% and 36% in the active and placebo groups, respectively. The relative risk of a patient experiencing PGIC ≥5 in the active group compared to the sham group with 95% confidence interval was 0.9 (0.6–1.4), $P = .667$.

CONCLUSIONS: Amputees with phantom limb pain treated with percutaneous cryoneurolysis rate analgesic improvements as clinically meaningful similar to pharmacologic treatments, although their MCID for the Brief Pain Inventory was somewhat larger than previously published values. This information on patient-defined clinically meaningful improvements will facilitate interpretation of available studies and guide future trial design. (Anesth Analg 2024;139:1325–31)

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KEY POINTS

- **Question:** After a nonpharmacologic analgesic intervention, what is the smallest meaningful improvement in pain scores (minimal clinically important difference [MCID]) and the Brief Pain Inventory measuring pain's interference in physical and emotional functioning?
- **Findings:** For amputees with phantom limb pain treated with ultrasound-guided percutaneous cryoneurolysis, median (interquartile range [IQR]) phantom pain numeric rating scale (NRS) (0–10) improvements at 4 months considered small, medium, and large were 1 [1–1], 3 [3–4], and 4 [3–6], respectively; and the median improvements in the Brief Pain Inventory interference subscale (0–70) associated with a small, medium, and large analgesic changes were 16 [6–18], 24 [22–31], and 34 [22–46].
- **Meaning:** Amputees with phantom limb pain treated with percutaneous cryoneurolysis rate analgesic improvements as clinically meaningful similar to pharmacologic treatments, although their MCID for the Brief Pain Inventory was somewhat larger than previously published values.

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommends the use of the numeric rating scale (NRS) to assess pain within clinical investigations,[1] and is applied nearly universally. Similarly, the IMMPACT also advocates the evaluation of impairment in physical and emotional functioning with an instrument such as the Brief Pain Inventory.[1] Considering both are recorded using an ordinal scale, statistical significance is frequently identified. However, what constitutes a *clinically meaningful* improvement to patients remains imperfectly defined.[2] Establishing the smallest clinically meaningful improvement—also termed minimal clinically important difference (MCID)—enables adequate prospective study design and powering, as well as the evaluation of previously published trial data.

The smallest clinically meaningful improvement may be calculated using an anchor-based method by correlating NRS and Brief Pain Inventory scores to patients' own assessment of their improvement, such as the Patient Global Impression of Change (PGIC) scale, as recommended by the IMMPACT.[1]

We therefore used an anchor-based method to reanalyze a recently published multicenter clinical trial involving the use of percutaneous cryoneurolysis to treat chronic postamputation phantom limb pain.[3] A prolonged neural block is provided with cryoneurolysis, which entails the application of very low temperatures (approximately −70°C using N_2O) to reversibly ablate peripheral nerves.[4] A total of 144 participants were enrolled in the original clinical trial and randomized to either active treatment or a sham procedure.[3] The difference between treatment groups was not statistically significant for the primary outcome measure—the change in average phantom pain intensity between baseline and 4 months as measured with an NRS (0–10); but the dataset nevertheless provides a valuable opportunity to help define the smallest clinically meaningful improvement in NRS and the Brief Pain Inventory.

METHODS

The original trial followed good clinical practice and was conducted within the ethical guidelines outlined in the Declaration of Helsinki. The trial was registered before patient enrollment (NCT03449667, principal investigator: B. M. Ilfeld, MD, MS; initial posting: February 28, 2018). The Institutional Review Board approved the protocol at each of the 6 enrolling centers as well as the United States Army Medical Research and Development Command Human Research Protection Office. An independent Data Safety Monitoring Board was responsible for the conduct and oversight of all aspects of the investigation. Written, informed consent was obtained from all participants. Deidentified data were used for the current secondary analysis.

Original Trial

Protocol details and results of the original trial have been published previously.[3] In short, patients with a lower-limb amputation and established phantom pain received a single-injection ropivacaine femoral and sciatic peripheral nerve block. They were subsequently randomized to receive either an ultrasound-guided percutaneous cryoneurolysis treatment or a sham procedure in a participant- and observer-masked fashion. The original primary outcome was the average intensity of phantom limb pain 4 months after the intervention as measured on a 0 to 10 NRS within the Brief Pain Inventory, short form. An optional crossover treatment 4 to 6 months after the initial intervention allowed all participants the opportunity to ensure

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Conflicts of Interest: See Disclosures at the end of the article.

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Clinical Trial Registration: This study was registered with the Clinical Trial Registry (NCT03449667, principal investigator: B. M. Ilfeld, MD, MS) on February 28, 2018, and can be reached at Clinicaltrials.gov.

Reprints will not be available from the authors.

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they received an active treatment, but because it was optional also introduced selection bias from this time point forward. Consequently, we now include only data collected at the 4-month primary outcome timepoint before the optional crossover intervention.

Current Analysis

To provide a global measure of worsening or improvement, the PGIC was administered, allowing patient evaluation of integrated treatment effects.[5] This measure is a 7-point ordinal scale requiring the patient to rate the current intensity of phantom limb pain compared to their pretreatment baseline: 1 for "very much worse" to 7 for "very much improved" (4 is "no change"). We used this scale to determine what the participants of our study considered small, medium, and large NRS improvements. Specifically, we report the change in average NRS pain score for each of 5 categories: worsening (PGIC = 1–3), no improvement (PGIC = 4), small improvement (PGIC = 5), medium improvement (PGIC = 6), and large improvement (PGIC = 7). We used a χ^2 test to examine the relationship between treatment (sham versus active) and any improvement defined by PGIC ≥5.

The primary instrument of the original investigation was the Brief Pain Inventory, short form, which assesses pain and its interference with physical and emotional functioning.[6] The form includes 3 domains: (1) pain, with 4 questions using an NRS to evaluate 4 pain levels: "current," "least," "worst," and "average"; (2) percentage of relief provided by pain treatments with 1 question; and (3) interference with physical and emotional functioning using a 0 to 10 scale (0 = no interference; 10 = complete interference). The 7 interference questions involve general activity, mood, walking ability, normal work activities (both inside and outside of the home), relationships, sleep, and enjoyment of life.[6] The 7 functioning questions can be combined to produce an interference subscale (0–70). The use of both single items (eg, mood) and the composite scores is supported by the IMMPACT recommendations for assessing clinical trials.[5,7]

The IMMPACT consensus statement specifies that "available data suggest that a change of 1 point on the Interference Scale [presumably for a single question]… would be a reasonable benchmark for future studies designed to identify minimally clinically important changes."[2] However, it also notes that "because few studies have examined the importance of worsening on these measures, *benchmarks* are only provided for improvement in scores [emphasis added]."[2] To define amputee-specific clinically meaningful improvements in the Brief Pain Inventory, we used the PGIC data to determine the change in total Brief Pain Inventory interference subscale (7 questions added together) that patients considered to be a worsening (PGIC = 1–3), no improvement (PGIC = 4), and small (PGIC = 5), medium (PGIC = 6), or large (PGIC = 7) improvement.

RESULTS

A total of 144 participants were enrolled in the original clinical trial and randomized to either active treatment (n = 71) or a sham procedure (n = 73; Figure 1).[3] The difference between treatment groups was not statistically significant for the primary and secondary outcome measures in the original trial. Eight participants did not have a PGIC recorded at month 4, and thus 136 participants were included in the current analysis.

The median (interquartile range [IQR]) phantom limb pain NRS improvements considered small, medium, and large by patients were 1 [1–1], 3 [3–4], and 4 [3–6], respectively (Table 1 and Figure 2). Based on the PGIC at 4 months, the median (IQR) Brief Pain Inventory (interference subscale) improvement considered small, medium, and large by patients was 16 [6–18], 24 [22–31], and 34 [22–46], respectively (Table 2). The proportions of patients that experienced PGIC ≥5 were 33% and 36% in the active and placebo groups, respectively. The relative risk of a patient experiencing PGIC ≥5 in the active group compared to the sham group with 95% confidence interval was 0.9 (0.6–1.4), $P = .667$.

DISCUSSION

This reanalysis of data from a previously published clinical trial identified that pain score decreases as little as 1 on the 0 to 10 NRS are deemed an improvement, albeit "small," requiring a fall of 3 to 4 points to be described as a "medium" or "large" improvement. These values for patients undergoing ultrasound-guided percutaneous cryoneurolysis are similar to IMMPACT "benchmarks" of 1, 2, and 4 points representing "minimally important but perhaps not very important," "much better," and "substantial" changes in pain, respectively.[2] However, these values were based on 3 analyses,[8–10] and the smallest clinically important improvement can be significantly influenced by numerous patient characteristics such as geographic locality,[11] culture,[11] ethnicity,[12] age,[13] sex,[8] body mass index,[13] educational level,[14] perceived general health,[14] disease and socioeconomic status,[15] psychological (depression, anxiety, catastrophizing, etc),[16,17] as well as pain baseline,[8] duration, intensity, frequency, location, and etiology.[2] Therefore, there are countless differing patient populations, requiring "confirmation in other patient populations and different chronic pain syndromes."[10]

Similarly, intervention tolerability, adverse effects, and safety all influence the evaluation of smallest clinically important improvements.[2,18] For

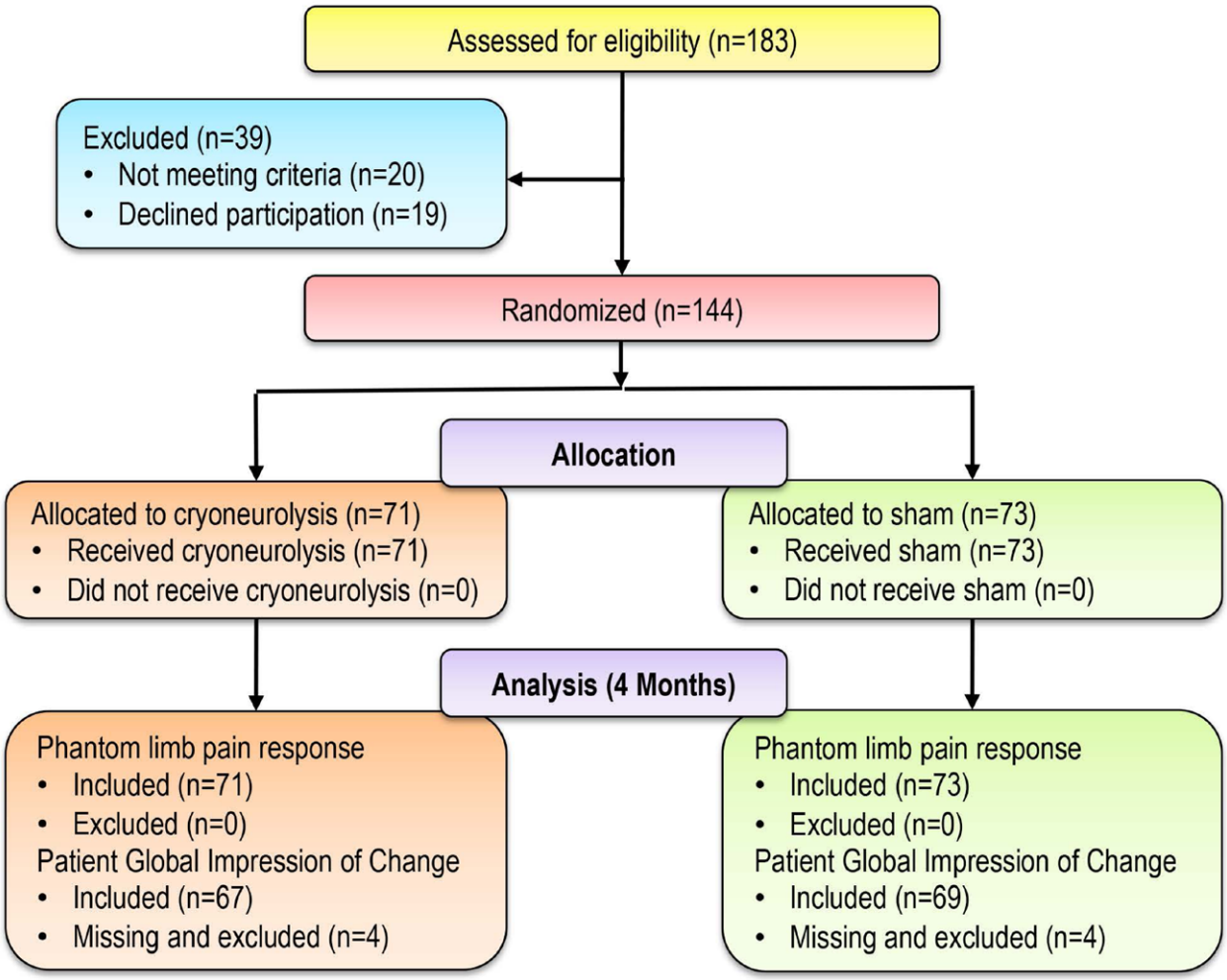

Figure 1. CONSORT diagram. CONSORT indicates Consolidated Standards of Reporting Trials.

example, a small analgesic benefit from a single minimally invasive procedure with few significant risks such as ultrasound-guided percutaneous cryoneurolysis may be deemed more acceptable than a similar benefit from a daily medication with systemic side effects such as pregabalin or opioids.[8,19] To our knowledge, this is the first effort to define the MCID after a device intervention (ultrasound-guided percutaneous cryoneurolysis). As noted by the IMMPACT, the duration of analgesic improvement should also be considered given that a small—yet long-lasting—analgesic benefit may be considered more acceptable than a similarly small benefit with a relatively short duration.[2] Perhaps as evidence of this concept, it is notable that the amputees of the current study considered the smallest important improvement to be a median (IQR) of 1.0 [0.5–1.3] on the NRS when measured 4 months after the cryoneurolysis treatment,[3] while a nearly identical patient population deemed the smallest MCID to be twice as great (2.0 [0–2.0]) when evaluated only 4 weeks after an ambulatory continuous peripheral nerve block.[20]

Table 1. Improvement in Average Phantom Pain at 4 mo Defined as Small, Medium, and Large by Participants Based on the PGIC

	Phantom Limb Pain Score Improvement (Numeric Rating Scale)				
PGIC Descriptor	**Worsening**	**None**	**Small**	**Medium**	**Large**
PGIC score	1–3	4	5	6	7
	(n = 4)	(n = 66)	(n = 8)	(n = 3)	(n = 45)
Mean (SD)	−0.4 (0.5)	0 (1.0)	1.0 (0.9)	3.1 (0.7)	4.5 (1.9)
Mean (95% CI)	−0.4 (−1.1 to 0.4)	0 (−0.2 to 2.0)	1.0 (0.2 to 1.8)	3.1 (2.2 to 4.0)	4.5 (3.9 to 5.2)
Median [IQR]	−0.3 [−0.6 to 0]	0 [−0.5 to 0.5]	1.0 [0.5 to 1.3]	3 [3.0 to 3.5]	4 [3.3 to 5.5]

Eight patients did not have a PGIC response and were excluded (n = 136).
Abbreviations: CI, confidence interval; SD, standard deviation; IQR, interquartile range [25th–75th percentiles]; PGIC, Patient Global Impression of Change.

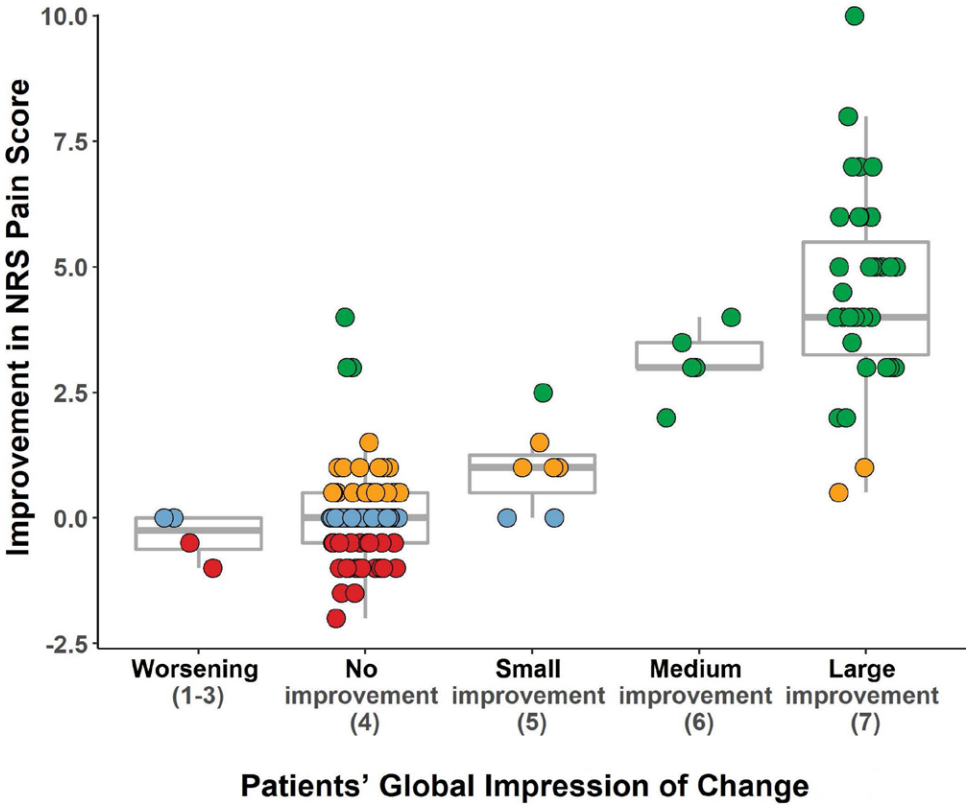

Figure 2. Improvement in average phantom pain as measured on a NRS defined by PGIC 4 mo after the intervention. Data expressed as median (dark horizontal bars) with IQR (Q1–Q3) (box), minimum between maximum value and Q3 + 1.5*IQR and maximum between minimum value and Q1 − 1.5*IQR (whiskers). Scatter points represent the data points color-coded by the level of improvement: worsening (red), no change (blue), improvement (orange), and clinically meaningful improvement (green). IQR indicates interquartile range; NRS, numeric rating scale; PGIC, Patient Global Impression of Change; Q, quartile.

Brief Pain Inventory

Compared with the NRS, there are far fewer published data reporting on the smallest improvement within the Brief Pain Inventory deemed important to patients. The current analysis identified the improvements in the Brief Pain Inventory's interference subscale (range 0–70) associated with small, medium, and large changes in pain scores as (median) 16, 24, and 34, respectively. These values somewhat surpass the "benchmark" smallest clinically meaningful improvement of 1 to 2 points for each scale (7–14 for the total of 7 items) originally cited in the IMMPACT recommendations.[2] Our findings are supported by 144 additional amputees of the previously mentioned study involving continuous peripheral nerve blocks which reported nearly identical values to those of the current analysis.[20]

Limitations

There are certain limitations to consider in this analysis. First, we present secondary outcomes that were not part of the original protocol and statistical plan, making this a retrospective analysis of prospectively collected data. Additionally, our results are applicable only to patients with postamputation phantom limb pain and may not be generalized to other common pain conditions. However, the specificity of our results to this particular population is also a strength of the study. Another limitation is that the PGIC question did not differentiate between phantom and residual limb pain, but rather encompassed pain in general. This is evident in Figure 2, where 3 participants reported their pain as unchanged on the PGIC, despite the actual phantom limb pain score improving by 3 or more points between baseline and

Table 2. Improvement in the Brief Pain Inventory Interference Subscale at 4 mo Defined as Small, Medium, and Large by Participants Based on the PGIC

	Brief Pain Inventory improvement (Interference subscale)				
PGIC descriptor	**Worsening**	**None**	**Small**	**Medium**	**Large**
PGIC score	1–3 (n = 4)	4 (n = 66)	5 (n = 8)	6 (n = 3)	7 (n = 45)
Mean (SD)	−9 (9)	1 (7)	11 (11)	23 (12)	33 (17)
Mean (95% CI)	−9 (−22 to −4)	1 (−1 to 3)	11 (1 to 22)	23 (8 to 38)	33 (27 to 39)
Median [IQR]	−8 [−14 to −2]	0 [−2 to 1]	16 [6 to 18]	24 [22 to 31]	34 [22 to 46]

Eight patients did not have a PGIC response and were excluded (n = 136).
Abbreviations: CI, confidence interval; SD, standard deviation; IQR, interquartile range [25th–75th percentiles]; PGIC, Patient Global Impression of Change.

4 months. Most participants experienced changes in both phantom and residual limb pain in the same direction (either improving or not), but a few cases demonstrated improvement in phantom pain alongside worsening in residual limb pain, leading the participant to respond that their overall "pain" had "worsened" (or vice versa). Last, there were few participants in the "small" and "medium" range of the PGIC relative to the number of participants rating their pain as unchanged or a "large" improvement, limiting our ability to identify the minimum clinically important difference for these subgroups.

In summary, patients with postamputation pain rate analgesic improvements as clinically meaningful, similar to other chronic pain conditions and pharmacologic interventions, although their smallest meaningful improvement within the Brief Pain Inventory was somewhat larger than the "benchmark" smallest clinically meaningful improvement originally cited in the IMMPACT recommendations. Determining clinically meaningful analgesic changes requires the study of populations with various pain conditions and different analgesic interventions. The results from this analysis will facilitate interpretation of data from published studies of similar populations and interventions, and guide future trial design by enabling investigators to adequately power future investigations. ■

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