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Primary Knee

Cryoneurolysis Associated With Improved Pain, Function, and Sleep in Patients Following total Knee Arthroplasty: Use of a New Real-World Registry

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ABSTRACT

Background: Total knee arthroplasty (TKA) is performed on approximately 790,000 patients annually in the United States and is projected to increase to 1.5 million by 2050. This study aimed at assessing the use of preoperative cryoneurolysis on patients undergoing TKA by analyzing: (1) pain severity; (2) opioid use; (3) functional status; and (4) sleep disturbance (SD) over 6 months following discharge.
Methods: Patients enrolled in the Innovations in Genicular Outcomes Registry between September 2021 and February 2024 were followed for 6 months. Our analyses included patients undergoing unilateral primary TKA with no preoperative opioid prescription, who either received cryoneurolysis, or did not. Baseline patient demographics were collected before TKA and tabulated. Pain management was assessed via the Brief Pain Inventory-Short Form instrument for pain severity. SD was measured using the patient-reported outcomes measurement information system questionnaire. Each outcome measure was assessed prior to TKA, weekly, and at monthly follow-up. Data were analyzed by a generalized linear

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patient-reported outcomes
multi-center registry

mixed-effect regression model to compare cryoneurolysis versus control patients, with a $P < .05$ as significant.

Results: There were 80 patients who were treated with preoperative cryoneurolysis, while 60 control patients did not have treatment. Patients receiving cryoneurolysis experienced significantly lower pain severity and SD over the 6-month follow-up than control patients ($P = .046$). Cryoneurolysis was also associated with a trend toward greater functional improvement that did not reach statistical significance ($P = .061$). Further, patients who underwent cryoneurolysis were 72% less likely than control group patients to take opioids over 6 months following discharge ($P < .001$).

Conclusions: Preoperative cryoneurolysis therapy in opioid-naive patients undergoing TKA is associated with improved pain, decreased opioid use, and improved SD for 6 months postoperatively. Cryoneurolysis, a nonopioid pain relief modality administered preoperatively, demonstrated substantial benefits in patients who underwent TKA.

Effective pain management is crucial for recovery and regaining functions after total knee arthroplasty (TKA) [1]. Better pain management is linked to enhanced patient outcomes, reduced recovery time, quicker rehabilitation, and a shorter hospital stay [2]. Effective analgesia also facilitates earlier ambulation, which further decreases hospital time and associated health care costs. Given the predicted rise in the frequency of TKA in the United States— from the current estimate of 790,000 primary TKAs to 1.5 million in the United States by 2050— optimizing perioperative pain control techniques before surgery is essential [3] to ensure optimal outcomes across this expanding population. Given the shortcomings and potential complications of prevalent treatments for chronic pain, there is a major interest in developing tailored multimodal treatment strategies that integrate nondrug-based therapies while advocating for nonopioid-based treatments.

Preoperative cryoneurolysis, a variant of cryotherapy, freezes peripheral sensory nerves in an effort to improve pain control before, during, and after surgery [4–7]. As a nonoperative, minimally invasive, and quick treatment, cryoneurolysis presents a valuable option for inclusion in a comprehensive treatment plan to alleviate knee pain from TKA [8]. The goal of percutaneous cryoneurolysis is to alleviate neuropathic pain after surgery by targeting the knee's sensory nerves, most commonly the medial or intermediate cutaneous branch of the anterior femoral cutaneous nerve, and the infrapatellar and sartorial branches of the saphenous nerve [5]. The technique cools these nerves, inducing controlled damage to the nerve axon and myelin sheath while sparing the epineurium and perineurium, facilitating axonotmesis and allowing for myelin and axon regeneration [9]. Typically, a trio of fine needles is applied to a concentrated area of superficial nerves, with consideration of further applying a single needle to the area of deep nerves [10]. One study demonstrated that patients who received preoperative cryoneurolysis 5 days before primary TKA had a 45% reduction in opioids relative to controls, earlier discharge by 2 days, and decreased pain levels overall [5]. However, there are no large-scale studies to date that have examined the use of cryoneurolysis to decrease pain and improve function and sleep disorder following primary TKA [9].

Randomized controlled trials are the gold standard to evaluate the safety and efficacy of new treatment options for knee osteoarthritis (OA) [11]. Yet they come with their own set of challenges, including practical and resource limitations, typically small participant groups, and limited generalizability due to strict selection criteria [12]. Conversely, retrospective studies that draw on administrative and claims databases may lack patient-reported outcomes (PROs), vital clinical details, and potential confounding variables, including disease severity, patient compliance, and the overall suitability of patients undergoing TKA [13,14].

Real-world registries offer a distinct perspective compared to administrative or claims-based studies, as they can reveal insights into physician and patient treatment preferences and how they are shaped by financial and reimbursement considerations not seen in clinical trials [15]. Moreover, unlike randomized controlled trials, which follow strict protocols, real-world registries have the flexibility to collect diverse datasets that more accurately reflect the perioperative management of TKA in everyday clinical practice. These registries can also be designed prospectively, allowing for data standardization, the inclusion of PROs, and other key health utilization metrics. The Innovations in Genicular Outcomes Registry (iGOR) is one such real-world registry [15] that employs a prospective observational study design to systematically capture data on various knee OA treatments, focusing on clinical effectiveness, safety, quality of life, and overall health care utilization.

The present study utilized the iGOR registry to characterize the effectiveness of cryoneurolysis as a preoperatively-administered pain control regimen among patients undergoing primary TKA by analyzing: (1) pain severity; (2) opioid usage; (3) functional outcome; and (4) sleep disturbance (SD).

Methods

Registry

The Innovations in Genicular Outcomes Registry (iGOR), registered on Clinicaltrials.gov (NCT05495334), is an ongoing, multicenter, prospective observational study to evaluate clinical and health outcomes for knee OA pain for as long as 18 months post-intervention [16]. To best replicate real-world practice, shared decision making dialogues between the attending physician and patient are the sole determinants of the clinical decisions captured in this observational registry. The iGOR records a comprehensive array of pain management strategies, from oral drugs like nonsteroidal anti-inflammatories and opioids, to denervation techniques like radiofrequency ablation and cryoneurolysis, various joint injections, and surgical interventions such as arthroplasty. Currently, the registry has recruited participants from 8 diverse sites, including both academic and outpatient settings (Campbell Clinic, Memphis, TN; Cedars Sinai Medical Center, Los Angeles, CA; Hoag Orthopedic Institute, Beverly Hills, California; Ortho West, Omaha, Nebraska; Mid State Orthopedics, Alexandria, Louisiana; Oschner Medical Center, New Orleans, Louisiana; and Sinai Hospital of Baltimore, Baltimore, MA), and is set to expand to 11 sites across the United States. The team of principal investigators boasts diverse expertize spanning orthopaedic surgery, sports medicine, pain management, and rheumatology. Each site is institutional review board-approved, adhering to standards set by the International

Conference on Harmonization, Good Clinical Practices, and Food and Drug Administration (FDA).

Individuals considered for the iGOR registry include patients preparing to undergo treatments for knee OA within 2 months of their initial assessment, who are capable of providing informed consent. Those actively participating in another investigational study that interferes with the standard of care or are planning a different surgery than the one on the knee in question are not eligible. Once enrolled in the iGOR registry, participants use web-based Health Insurance Portability and Accountability Act -compliant tools on their smartphones to record PROs prior to treatment at study enrollment (baseline) and during follow-up periods of up to 18 months after the first treatment. If patients undergo subsequent treatments, their follow-up in the registry extends a further 18 months from their latest treatment date.

Patient Cohorts

We identified patients who underwent unilateral primary TKA between September 1, 2021, and February 1, 2024, with at least 30 days and up to 6 months of follow-up from the iGOR registry. Patients were included if they were not prescribed opioids the night before surgery or in the preoperative area. Patients were further divided based on whether they did or did not receive cryoneurolysis within 30 days preoperatively (cryoneurolysis versus control patients). Cryoneurolysis involved the administration of Iovera (Pacira BioSciences, Parsippany, NJ), a handheld device that applies freezing cold to peripheral nerves aimed at blocking or relieving pain [17]. It involves administration of cryogen (nitrous oxide) through a 20-gauge, 90-millimeter (mm) closed-end needle or three 8.5-mm, 27-gauge needles following local anesthesia, with lidocaine aimed toward the superficial genicular nerves (infrapatellar saphenous nerve , anterior or lateral femoral cutaneous nerve, or the deep genicular nerves (inferior medial or lateral genicular nerve, superior medial or lateral genicular nerve, which innervate the anterior or lateral knee overlying the surgical site. In general, Iovera administration involves the identification of nerves through landmark and ultrasound methods, and it takes approximately 30 min to complete.

Baseline patient demographics and medical history were collected, including age, sex, body mass index (BMI), lifestyle factors, Kellgren-Lawrence (KL) score [18], knee OA treatment history, American Society of Anesthesiologists (ASA) classification, baseline pain catastrophizing scale score, and baseline outcome measures.

Pain Control Assessment

The pain levels were assessed through 2 measures: (1) the Brief Pain Inventory-Short Form (BPI-SF) [19,20]; (2) a personal log of pain relief medications taken, including both opioid and nonopioid drugs. The pain severity outcome was scored based on items #3 to #6 from the BPI-SF, each of which ranged from 0 (no pain) to 10 (unimaginable pain) and was documented by patients at baseline, weekly, and monthly during follow-up. Specifically, this modified scoring system included overall pain intensity at its worst, at its least, on average, and at the time of recording (Supplementary Figure 1) [21,22]. Opioid use was self-reported by patients, which was compiled into the iGOR system and inputted on a monthly schedule.

Functional Assessment

Functional assessment primarily utilized the Knee Injury and Osteoarthritis Outcome Scores, Joint Replacement (KOOS, JR) [23] questionnaire at the initial visit and subsequently on a weekly and monthly basis. The KOOS, JR consists of 7 questions designed to assess a person's knee health, assessing the extent of knee stiffness, pain intensity, and the individual's capacity to carry out daily tasks. Scoring for KOOS, JR, ranged from 0, indicating the best possible condition, to 4 denoting severe impairment, with a total score range of 0 to 28 [24]. This total score was converted to a normalized interval score with a standard deviation of 10, 50 considered the average joint health, and 100 as perfect joint health.

Sleep Disturbance (SD) Assessment

Sleep-related disturbance was documented based on the Patient-Reported Outcomes Measurement Information System SD short form 8b instrument, assessing patients' perceptions of sleep quality, sleep depth, and restoration associated with sleep over the past 7 days [25]. This instrument comprised 8 items, which were summed (range, 8 to 40; higher score: more disturbed sleep) and normalized into a *T* score, with a mean of 50 representing the average SD in the general population and a standard deviation of 10. A T score of 60 suggests one standard deviation worse than the average.

Data Analyses

Descriptive statistics were used to characterize the baseline characteristics of cryoneurolysis and control patients, respectively, including patient demographics and medical history. Differences between cohorts were evaluated using *Chi*-square tests for categorical variables and Kruskal-Wallis tests for continuous variables.

To evaluate post-TKA outcomes of pain control, physical function, and SD for a 6-month period, an overall trend analysis was performed by accounting for all follow-up outcome measures. Changes or improvements in post-TKA outcome scores from baseline measures were assessed over a 6-month period. Moreover, a minimal clinically important difference (MCID) score was determined based on a patient-defined cutoff value (ie, Kazis-effect size). For all analyses, multivariable generalized linear mixed-effect regression modeling was conducted to compare outcomes of pain severity, opioid use, functional status, and SD between cryoneurolysis and control cohorts; a normal distribution was applied to analyses of trend and outcome score changes from baseline, and a binomial distribution was used for the status of opioid use and achieving MCID. Analytical models comparing cryoneurolysis versus control patients were adjusted for cofounders, including certain baseline patient characteristics (age, sex, BMI, KL-grade, ASA), the baseline score on the pain catastrophizing scale, and the respective baseline outcome score.

All statistical analyses were conducted using Statistical Analysis Software (SAS) version 9.4 (SAS Institute, Cary, NC). The cut-off for statistical significance was set at 0.05.

Baseline Characteristics

A total of 140 patients who were not prescribed opioids preoperatively were followed for an average of 143 days after TKA (Table 1). There were 80 patients treated with cryoneurolysis between 4 and 23 days preoperatively to potentially decrease postoperative pain. Overall, patients had an average age of 66 years (standard deviation 9), with a majority being women (64%), obese (mean BMI 30, range, 16 to 47), bearing a KL-grade of 4 (93%), and in manageable to good health (ASA I or II: 74%) (Table 2). At baseline, patients in both cohorts reported moderate pain severity (mean: 4.67), worse than average physical function (mean: 49.76), and worse than average SD (mean: 54.37).

Table 1
The Cohort Attrition.

Step	Description	N	%
0	All enrolled patients as of 02/01/2024	10,63	100.0
1	Patients who received total knee arthroplasty (TKA)	258	100.0
2	With primary TKA on the target knee	252	97.7
3	With ≥30 d of follow up	231	91.7
4	With unilateral TKA	219	94.8
5	With unilateral knee OA diagnosis	215	98.2
6	With available follow-up outcomes	204	94.9
7	Free of presurgical opioid use (final study cohort)	140	68.6

TKA, total knee arthroplasty; OA, osteoarthritis.

Results

Enhanced Recovery after Surgery and Length of Facility Stay

A similar distribution of several enhanced recovery after surgery components was observed between the 2 cohorts. The frequency of use in cryoneurolysis compared to control cohorts was: 10 versus 15% (perioperative corticosteroids), 56 versus 33% (tranexamic acid), 25 versus 32% (antiemetics), 0 versus 17% (urinary catheter), 21 versus 18% (antithrombotic agent), and 81 versus 88% (preoperative nonopioid analgesics). Opioid use was low during the intraoperative period (17 versus 25%). However, postoperative opioid use was identified in only half of the patients treated with cryoneurolysis (51%) over the follow-up period, but among almost all control patients (98%). Some form of nerve block was also administered to at least 95% of patients in both cohorts.

Facility stay among patients in each cohort was <1 day; the average length of stay was 17.2 and 20.6 h in the cryoneurolysis and control cohorts, respectively.

Postoperative BPI-SF Pain Severity over 6 Months in Cryoneurolysis versus Control Cohorts

A reduction in pain severity apparent began at week 1 following TKA in both cohorts; the least square mean (LSM) and standard error (SE) for pain severity at week 1 were 3.82 (0.57) in the cryoneurolysis cohort and 4.64 (0.64) in the control cohort. Over 6 months of follow-up, there was a significant trend toward decreased pain severity in both cohorts ($P < .001$; Figure 1). However, patients treated with preoperative cryoneurolysis had significantly lower pain severity over time than controls; the overall LSM (SE) for pain severity was 2.45 (0.55) and 3.07 (0.49) in the cryoneurolysis and control cohorts, respectively ($P = .024$).

When the extent of change between postoperative and preoperative pain severity was compared, the cryoneurolysis cohort experienced significantly more pain reduction from the preoperative level than the control cohort (LSM [95% confidence interval {CI}] for pain reduction: 2.35 [0.73 to 3.97] versus 1.57 [0.13 to 3.01], $P = .049$) (Supplementary Table 1).

Status of Achieving MCID in Postoperative Pain Severity over 6 Months in Cryoneurolysis versus Control Cohorts

In the 6 months postoperatively, there was an increase in the number of patients who achieved pain relief at a MCID in both cohorts, with the highest proportion of patients at 6 months (81% in patients who received cryoneurolysis versus 73% in controls) (Table 3). Overall, the cryoneurolysis cohort was 55% more likely than controls to achieve MCID for pain reduction than the control cohort (overall proportion: 71 versus 62%; OR [95% CI]: 1.55 [1.15 to 2.07], $P = .004$).

Table 2
Baseline Characteristics of the Study Patients.

	Cryoneurolysis (N = 80)	Control (N = 60)	Total (N = 140)	*P* Value
Follow-up time since TKA (day)	143.94 (55.84)	142.10 (52.69)	141.35 (54.32)	.8047
Age, mean (SD)	66 (9.95)	65 (6.87)	66 (8.76)	.0563
Sex, N (%)				.447
Women	53 (66)	36 (60)	89 (64)	
Men	27 (34)	24 (40)	51 (36)	
Race/Ethnicity, N (%)				.011
Asian	1 (1)	3 (5)	4 (3)	
Black or African American	13 (16)	0	13 (9)	
Other/Unknown	8 (10)	9 (15)	17 (12)	
White	58 (73)	48 (80)	106 (76)	
BMI, mean (SD)	30.83 (6.35)	29.45 (6.32)	30.24 (6.35)	.2384
KL grade, N (%)				.0339
2 (Mild)	0	3 (5)	3 (2)	
3 (Moderate)	2 (3)	5 (8)	7 (5)	
4 (Severe)	78 (98)	52 (87)	130 (93)	
History of alcohol or substance abuse, N (%)				.8371
No	79 (99)	59 (98)	138 (99)	
Yes	1 (1)	1 (2)	2 (1)	
ASA classification, N (%)				.0942
I	26 (33)	30 (50)	56 (40)	
II	30 (38)	18 (30)	48 (34)	
III	24 (30)	11 (18)	35 (25)	
IV	0	1 (2)	1 (1)	
Baseline PCS	19.04 (14.43)	15.62 (9.05)	17.57 (12.49)	.5867
Baseline pain severity (BPI-SF)	4.93 (2.47)	4.33 (1.96)	4.67 (2.28)	.1714
Baseline physical function (KOOS, JR)	48.21 (17.0)	51.84 (12.38)	49.76 (15.25)	.4463
Baseline SD (PROMIS-SD (8b))	54.79 (9.47)	53.80 (8.26)	54.37 (8.95)	.3726

TKA, total knee arthroplasty; BMI , body mass index; KL, Kellgren-Lawrence; ASA, American Society of Anesthesiologists; PCS, Pain Catastrophizing Scale; BPI-SF, brief pain inventory-short form; KOOS, JR, knee injury and osteoarthritis outcome scores, joint replacement; PROMIS-SD, patient-reported outcomes measurement information system sleep disturbance.

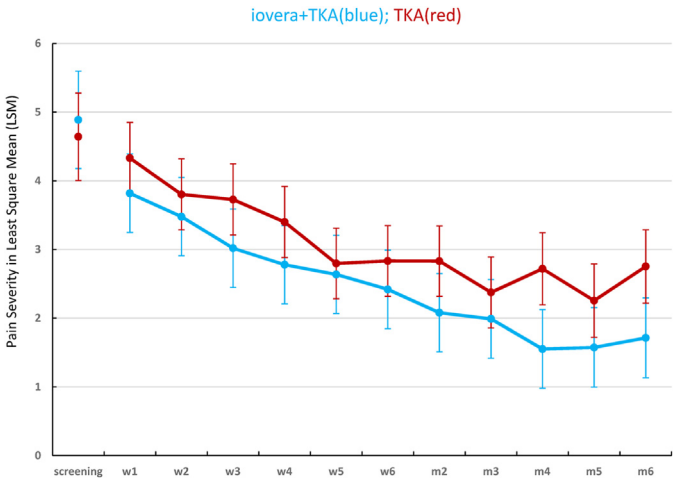

Fig. 1. BPI-SF Pain Severity Scores over 6-month Follow-Up after Discharge; Error Bar: standard error of the least square mean (LSM).*,** Pain Severity in least square mean (LSM) *. The lower the LSM, the less pain severity. **. Adjusted for age, sex, BMI, ASA, KL-grade, baseline PCS, baseline pain severity score. BPI-SF, brief pain inventory-short form; TKA, total knee arthroplasty; BMI, body mass index; ASA, American Society of Anesthesiologists; KL, Kellgren-Lawrence; PCS, pain catastrophizing scale.

Use of Opioids over 6 Months Postoperatively in Cryoneurolysis versus Control Cohorts

Substantially, more control patients reported using opioids than patients treated with cryoneurolysis at 1 month (46% in cryoneurolysis versus 83% in control cohorts) and 2 months (9 versus 26%) post-operatively (Table 4). The reported use of opioids decreased from 3 to 6 months postoperatively in both cohorts (<14%). Overall, patients who had cryoneurolysis were 73% less likely than controls to report postoperative opioid use (odds ratio [OR; 95% CI]: 0.27 [0.19 to 0.38], $P < .001$).

Postoperative KOOS, JR Functional Outcome over 6 Months in Cryoneurolysis versus Control Cohorts

Patients in both cohorts experienced functional improvement beginning at 1 week postoperatively in the cryoneurolysis cohort [LSM (SE): 50.54 (3.72)] and at 2 weeks in the control cohort [52.9 (3.71)]. Overall, there was a clear trend of functional improvement over time in both cohorts (Figure 2). Specifically, the cryoneurolysis cohort showed a trend toward greater improvement than the control cohort; the overall LSM (SE) for function was 64.60 (3.59) and 61.31 (3.19) for the cryoneurolysis and control cohorts, respectively ($P = .061$). When the postoperative and preoperative functional scores of the 2 cohorts were compared, a statistically similar degree of improvement was observed: LSM (95% CI) was 16.77 (6.88 to 26.67) in cryoneurolysis versus 13.63 (4.85 to 22.41) in controls ($P = .194$) (Supplementary Table 2).

Six-Month Postoperative Function MCID Achievement among Cryoneurolysis versus Control Cohorts

Both cohorts demonstrated a progressive temporal increase in the number of patients exceeding MCID for improved function, with the highest proportion at 6 months (95% in cryoneurolysis versus 98% in the control cohort) (Table 5). Overall, however, both cohorts yielded the same percentage of patients achieving the MCID for function (overall proportion: 87 versus 87%; OR [95% CI]: 0.94 [0.62 to 1.41]; $P = .761$).

Cryoneurolysis versus Control Cohort Patient-Reported Outcomes Measurement Information System-SD Trend in the 6 Months Postoperatively

As seen in Figure 3, at 2 months postoperatively, patients first demonstrated similar sleep quality to the general population in the cryoneurolysis cohort (LSM [SE] for SD: 50.25 [2.35]), while this occurred at 3 months in the control cohort (LSM [SE] for SD: 49.05

Table 3
Proportion (%) of Patients Achieving Minimal Clinically Important Difference (MCID) for Pain Severity Outcome Over 6-Mos Follow-Up After Discharge[a,b].

Time	Mean Difference from baseline[a,b]	Baseline SD	MCID	Estimate	Cohort	
					Cryoenurolysis	Control
w1				N (%) respondents	65 (81)	44 (73)
	−0.24	2.28	−0.11	% achieving MCID	54.2	48.8
w2				N (%) respondents	66 (83)	50 (83)
	−0.82	2.28	−0.36	% achieving MCID	64.9	53.1
w3				N (%) respondents	60 (75)	45 (75)
	−1.15	2.28	−0.50	% achieving MCID	60.8	54.8
w4				N (%) respondents	65 (81)	44 (73)
	−1.46	2.28	−0.64	% achieving MCID	68.9	62.3
w5				N (%) respondents	69 (86)	51 (85)
	−1.76	2.28	−0.77	% achieving MCID	66.1	58.9
w6				N (%) respondents	58 (73)	49 (82)
	−1.93	2.28	−0.85	% achieving MCID	71.5	65.3
m2				N (%) respondents	67 (84)	54 (90)
	−2.12	2.28	−0.93	% achieving MCID	80.4	65.5
m3				N (%) respondents	60 (75)	48 (80)
	−2.40	2.28	−1.05	% achieving MCID	75.1	65.5
m4				N (%) respondents	53 (66)	36 (60)
	−2.53	2.28	−1.11	% achieving MCID	80.3	60.2
m5				N (%) respondents	45 (56)	30 (50)
	−2.71	2.28	−1.19	% achieving MCID	78.2	73.4
m6				N (%) respondents	41 (51)	29 (48)
	−2.51	2.28	−1.10	% achieving MCID	80.9	72.7
Overall				% achieving MCID	71.7	62.2

BMI, body mass index; ASA, American Society of Anesthesiologists; KL, Kellgren-Lawrence; PCS, pain catastrophizing scale.
[a] MCID (Kazis-Effect Size) = group mean difference from baseline/group baseline SD.
[b] Adjusted for age, sex, BMI, ASA, KL-grade, and baseline PCS.

Table 4
Opioid Use (%) Over 6 Months Following Discharge[a,b].

	Cryoneurolysis		Control	
	N (%) Respondents	% Opioid Use	N (%) Respondents	% Opioid Use
w1	66 (83)	76.7	45 (75)	95.5
w2	67 (84)	63.9	50 (83)	94.5
w3	62 (78)	48.0	46 (77)	84.9
w4	64 (80)	45.7	45 (75)	73.5
w5	69 (86)	34.4	51 (85)	66.9
w6	58 (73)	31.3	49 (82)	60.7
m2	67 (84)	17.7	54 (90)	56.1
m3	60 (75)	24.3	48 (80)	32.3
m4	53 (66)	7.6	36 (60)	27.1
m5	45 (56)	15.0	30 (50)	19.7
m6	41 (51)	14.5	29 (48)	24.3
Overall		31.4		62.8

BMI, body mass index; KL, Kellgren-Lawrence; ASA, American Society of Anesthesiologists; PCS, pain catastrophizing scale.
[a] Least square mean for opioid use.
[b] Adjusted for age, sex, BMI, KL-grade, ASA, baseline PCS.

[2.15]). Overall, there was a trend toward diminishing SD in both cohorts in the 6 postoperative months of follow-up (Figure 3). Specifically, patients treated with cryoneurolysis experienced significantly greater sleep improvement than control patients (overall LSM (SE): 50.74 (2.27) versus 52.92 (2.02); $P = .046$). A similar observation of greater postoperative sleep improvement (less SD) was noted in the cryoneurolysis cohort than the control cohort (LSM (95% CI) for follow-up SD changes from baseline: 6.67 (1.34 to 11.92) versus 4.42 (−0.27 to 9.12); $P = .09$) (Supplementary Table 3).

MCID in Postoperative SD over 6 Months in Cryoneurolysis versus Control Cohorts

During follow-up, more than half of the patients achieved the MCID for sleep improvement at 4 weeks in cryoneurolysis and at 3 months in the control cohort (Table 6). Overall, the cryoneurolysis cohort had significantly greater odds than the control cohort of achieving the MCID for sleep outcome by follow-up (overall proportion: 62 versus 49%; OR [95%CI]: 1.70 [1.28 to 2.26], $P < .001$).

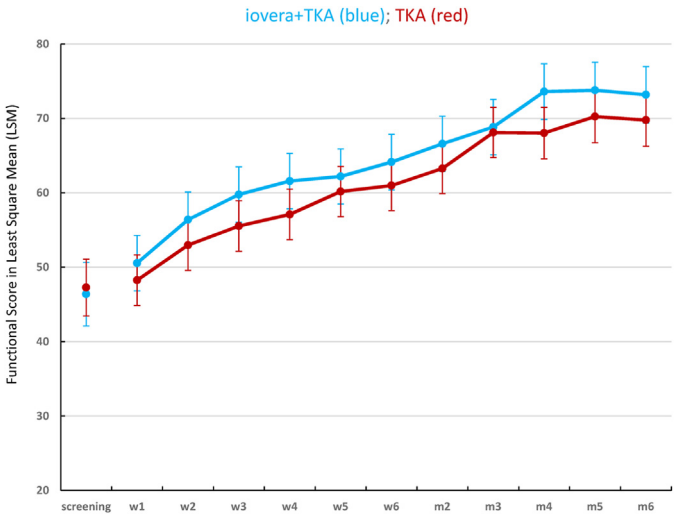

Fig. 2. KOOS, JR Functional (Interval) Scores over 6-month Follow-Up after Discharge; Error Bar: standard error of the least square mean (LSM).*,** Functional score in least square mean (LSM) *. The higher the LSM, the greater the functional status. **. Adjusted for age, sex, BMI, ASA, KL-grade, baseline PCS, baseline functional score. KOOS, JR, knee injury and osteoarthritis outcome scores, joint replacement; TKA, total knee arthroplasty; BMI, body mass index; ASA, American Society of Anesthesiologists; KL, Kellgren-Lawrence; PCS, pain catastrophizing scale.

Discussion

This study aimed at assessing the effects of preoperative cryoneurolysis on opioid-naive patients undergoing TKA by analyzing pain scores, opioid use, functional status, and SD over the 6 months post-operatively. Our data demonstrated that patients who received cryoneurolysis had improved pain at all weekly time points up to 6 months. Furthermore, patients receiving cryoneurolysis were 73% less likely than controls to take opioids during follow-up. Similar findings on SD and functional status were observed, with patients receiving cryoneurolysis experiencing a significant reduction in SD and a trend toward improvement in functional status relative to control patients. Overall, our data demonstrates that cryoneurolysis, a preoperative pain relief modality, is associated with improved pain, SD, and functional outcome for 6 months following unilateral primary TKA.

Pain management is among the most important elements of a comprehensive approach to optimizing ambulation, range of motion, and overall patient satisfaction following a primary TKA [26]. In particular, approaches that minimize opioid reliance in the postoperative period are critically important, as extended use of these drugs following TKA is associated with increased stiffness, diminished functional outcomes, and reduced quality of life [26,27]. Accordingly, a wide range of treatment strategies, including the use of nonsteroidal anti-inflammatory drugs, gabapentinoids, acetaminophen, local injections around the surgical site, and spinal anesthesia, have been investigated in an effort to lower opioid use while maintaining rehabilitation effectiveness [28,29]. However, such treatment options often only provide brief relief. In contrast, cryoneurolysis has the potential to deliver pain relief that lasts several weeks to months after surgery.

Cryoneurolysis is a pain management technique involving the application of extreme cold to inactivate sensory nerves to reduce pain [7,30,31]. The procedure is minimally invasive, targeting nerves with a cold application to block pain signals. Benefits reported in recent studies include reduced need for opioids, improved postoperative mobility, and faster recovery [31–33]. There are minimal adverse events, with adverse events accounting for approximately 1.1%, including skin infection, bruising or swelling, nerve pain or dysesthesia, and muscle cramping [30,34,35]. Of note, in our study, there were no reported adverse events attributed to Cryo usage. However, there was one patient who reported “nausea and vomiting after Iovera treatment.” The site considered this to be due to unknown factors “unrelated to Iovera treatment; possibly other unknown issue, according to the site principal investigator.” This event was resolved later on the same day.

In addition to pain relief, our study also found that cryoneurolysis could potentially improve early post-operative functional status in patients undergoing primary TKA who did not take preoperative opioids. With pain more effectively managed, patients can participate more fully and comfortably in physical therapy, leading to improved joint mobility, knee strength, and a quicker return to daily activities [36]. In one study, at a 6-week postoperative check-up, patients treated with cryoneurolysis exhibited a significant increase of 12 degrees in knee range of motion from presurgery levels, indicating less restriction from postoperative pain and muscle spasms [30]. Patients who received cryoneurolysis walked an average of 100 feet more than controls, suggesting a potential for enhanced endurance and strength for physical therapy engagement [26]. Such improvement in early

Table 5
Proportion (%) of Patients Achieving Minimal Clinically Important Difference (MCID) for Functional Outcome Over 6-Mos Follow-Up After Discharge[a,b].

Time	Mean Difference from baseline[a,b]	Baseline SD	MCID	Estimate	Cohort	
					Cryoneurolysis	Control
w1				N (%) respondents	66 (83)	44 (73)
	−0.82	15.25	−0.05	% achieving MCID	56.4	58.0
w2				N (%) respondents	67 (84)	50 (83)
	4.81	15.25	0.32	% achieving MCID	65.5	56.3
w3				N (%) respondents	62 (78)	46 (77)
	8.25	15.25	0.54	% achieving MCID	76.3	76.3
w4				N (%) respondents	64 (80)	45 (75)
	10.30	15.25	0.68	% achieving MCID	76.6	80.0
w5				N (%) respondents	69 (86)	51 (85)
	11.84	15.25	0.78	% achieving MCID	82.9	78.8
w6				N (%) respondents	58 (73)	49 (82)
	13.77	15.25	0.90	% achieving MCID	84.4	83.0
m2				N (%) respondents	67 (84)	54 (90)
	16.07	15.25	1.05	% achieving MCID	89.2	85.3
m3				N (%) respondents	60 (75)	48 (80)
	19.65	15.25	1.29	% achieving MCID	92.8	95.8
m4				N (%) respondents	53 (66)	36 (60)
	22.66	15.25	1.49	% achieving MCID	95.4	95.4
m5				N (%) respondents	45 (56)	30 (50)
	23.68	15.25	1.55	% achieving MCID	96.2	96.3
m6				N (%) respondents	41 (51)	29 (48)
	23.70	15.25	1.55	% achieving MCID	95.4	98.2
Overall				% achieving MCID	86.6	87.3

BMI, body mass index; ASA, American Society of Anesthesiologists; KL, Kellgren-Lawrence; PCS, pain catastrophizing scale.
[a] MCID (Kazis-Effect Size) = group mean difference from baseline/group baseline SD.
[b] Adjusted for age, sex, BMI, ASA, KL-grade, baseline PCS.

postoperative mobility is often hindered by the side effects of high opioid consumption, such as nausea and sedation [26].

Sleep disturbance is common among patients who have OA. In the Johnston County osteoarthritis project, 76% of patients who have symptomatic knee or hip OA reported insufficient sleep or insomnia [37]. In another observational study of patients who have a knee OA diagnosis, 31% reported problems with sleep initiation, and 81% had difficulties maintaining nighttime sleep [38]. In accordance with those results, patients in the present study demonstrated substantial SD at baseline (average T score: 60, one standard deviation above the mean). In the 2 months following TKA, sleep problems gradually improved to normal in patients treated with cryoneurolysis, while this improvement required 3 months among controls. Ample evidence suggests that sleep problems and pain are causally related, likely bidirectionally [38–41]. In particular, patients in major pain tend to develop SD, and those patients who have SD are more likely to either develop pain or to experience worsening of preexisting chronic pain. A similar improvement in both pain severity and SD over time was observed in the iGOR patients in the present study. While preoperative cryoneurolysis was effective for both outcomes, the improvement was more pronounced for pain severity.

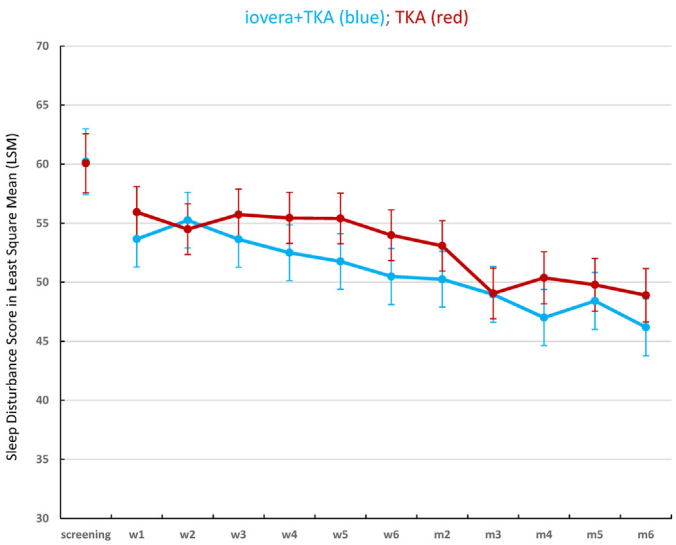

Fig. 3. PROMIS-SD, Sleep Disturbance (SD) T Scores over 6-month Follow-Up after Discharge; Error Bar: standard error of the least square mean (LSM).*,** SD score in least square mean (LSM) *. The lower LSM, the less SD. **. Adjusted for age, sex, BMI, ASA, KL-grade, baseline PCS, baseline SD score. PROMIS-SD, patient-reported outcomes measurement information system sleep disturbance; TKA: total knee arthroplasty; BMI, body mass index; ASA, American Society of Anesthesiologists; KL, Kellgren-Lawrence; PCS, pain catastrophizing scale.

There is evidence that cryoneurolysis also decreases pain in surgeries other than TKA [35]. In shoulder arthroplasty and rotator cuff repairs, cryoneurolysis has been used for long-term pain relief, enhancing recovery, and reducing reliance on pain medications [42]. The use of ultrasound-guided percutaneous cryoneurolysis of the suprascapular nerve resulted in pain scores consistently <2 points (on a visual analogue scale) and decreased opioid intake after shoulder surgery [42]. For thoracotomies, its application intraoperatively for the intercostal nerve has been associated with improved postoperative incisional pain and decreasing opioid use (661 versus 855 mg, $P < .05$), facilitating easier breathing and mobility [43]. Additionally, in the context of mastectomies, there is evidence that the use of cryoneurolysis on the intercostal nerve is associated with significantly diminished pain. Several case reports have demonstrated complete elimination of postoperative pain without any use of supplemental opioids [35,44]. Overall, the application of cryoneurolysis in acute pain management has continued to expand, partially with the advent of ultrasound guidance, which enables precise localization of the specific nerves of interest.

The present study has several potential limitations, many of which are inherent to observational registry-based analyses. Due to the lack of randomization or stratification, patients were not organized into treatment groups in a controlled manner. This led to

Table 6
Proportion (%) of Patients Achieving Minimal Clinically Important Difference (MCID) for Sleep Disturbance Outcome Over 6-Mos Follow-Up After Discharge[a,b].

Time	Mean Difference from baseline[a,b]	Baseline SD	MCID	Estimate	Cohort	
					Cryoneurolysis	Control
w1				N (%) respondents	63 (79)	44 (73)
	3.40	8.95	0.38	% achieving MCID	53.4	37.2
w2				N (%) respondents	66 (83)	50 (83)
	3.98	8.95	0.44	% achieving MCID	46.7	38.1
w3				N (%) respondents	61 (76)	45 (75)
	3.32	8.95	0.37	% achieving MCID	46.6	47.4
w4				N (%) respondents	63 (79)	44 (73)
	2.30	8.95	0.26	% achieving MCID	55.4	41.8
w5				N (%) respondents	67 (84)	50 (83)
	2.07	8.95	0.23	% achieving MCID	58.2	35.3
w6				N (%) respondents	57 (71)	49 (82)
	1.01	8.95	0.11	% achieving MCID	62.1	41.4
m2				N (%) respondents	66 (83)	54 (90)
	−0.04	8.95	0.00	% achieving MCID	65.2	38.0
m3				N (%) respondents	60 (75)	48 (80)
	−2.64	8.95	−0.29	% achieving MCID	67.8	68.8
m4				N (%) respondents	53 (66)	36 (60)
	−3.29	8.95	−0.37	% achieving MCID	76.8	61.2
m5				N (%) respondents	45 (56)	30 (50)
	−2.96	8.95	−0.33	% achieving MCID	69.7	61.2
m6				N (%) respondents	41 (51)	29 (48)
	−4.75	8.95	−0.53	% achieving MCID	76.6	70.1
Overall				% achieving MCID	62.2	49.2

BMI, body mass index; ASA, American Society of Anesthesiologists; KL, Kellgren-Lawrence; PCS, pain catastrophizing scale.
[a] MCID (Kazis-Effect Size) = group mean difference from baseline/group baseline SD.
[b] Adjusted for age, sex, BMI, ASA, KL-grade, baseline PCS.

an uneven distribution of patient numbers across treatments and variation in treatment numbers by site and subspecialty. Such variance poses difficulties in analyzing predetermined comparisons across specific treatments. Furthermore, the possibility of bias influencing a provider's choice of treatment for a certain patient population cannot be discounted. Nevertheless, it is worth noting that such a scenario may alternatively be viewed as the strength of this analysis as it most closely replicates the "real-world" environment [15]. The innovative use of this real-world registry enables the gathering of extensive data from actual clinical practices. Other potential biases include reporting bias and the Hawthorne effect [45], wherein patients alter their behavior because they know they are being observed, a factor that may be hard to quantify or counteract in an observational trial. Moreover, each participating site, ranging from academic medical centers to private clinics, manages the registry operations independently, without the direct oversight of a contract research organization, potentially leading to selection bias based on factors such as staff availability and data collection resources. Additionally, the use of technology (eg, smart phones) to collect data may bias our data against a representative sample of the clinic populations, such as patients from lower socioeconomic strata with less robust education who are less likely to have access to and be familiar with the technology required by the study design. In addition, as an observational registry, iGOR does not characterize the costs of specific treatments to patients or providers, detail differences in treatment administration (eg, time of administration, sites targeted), or document any associated adverse events. This would be an area for potential future study. It should be noted that for this study, the proportion of patients meeting MCID for functional improvement was statistically but not clinically significant, highlighting the importance of interpreting these results in an appropriate clinical context. Despite these issues, the use of the iGOR registry offers distinct advantages as a multicenter, prospective observational registry that captures comprehensive data on a variety of treatments for knee OA, including their clinical efficacy and PROs.

Conclusions

The present study was conducted to evaluate the impact of administering preoperative cryoneurolysis on opioid-naive patients undergoing TKA by examining pain levels, opioid use, functional outcome, and SD. Patients treated with cryoneurolysis reported less pain for up to 6 months postsurgery. These patients also showed substantially less use of opioids over the 6 months of postoperative observation. Similarly, preoperative cryoneurolysis improved functional outcomes and reduced SDs. In summary, preoperatively administered cryoneurolysis can lead to better outcomes in postoperative pain management, functional recovery, and SDs over at least 6 months in patients undergoing TKA.

CRediT authorship contribution statement

Michael A. Mont: Writing – review & editing, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jennifer H. Lin:** Writing – review & editing, Software, Resources, Methodology, Investigation, Formal analysis, Data curation. **Andrew I. Spitzer:** Writing – review & editing, Visualization, Validation, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Vinod Dasa:** Writing – review & editing, Visualization, Resources, Methodology, Investigation, Conceptualization. **Adam Rivadeneyra:** Writing – review & editing, Visualization, Resources, Project administration. **David Rogenmoser:** Writing – review & editing, Validation, Investigation, Data curation, Conceptualization. **Andrew L. Concoff:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Formal analysis. **Mitchell K. Ng:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mary DiGiorgi:** Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis,

Data curation. **Stan DySart:** Writing – review & editing, Visualization, Supervision, Software, Resources, Investigation, Funding acquisition, Formal analysis, Data curation. **Joshua Urban:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **William M. Mihalko:** Writing – review & editing, Visualization, Supervision, Project administration, Methodology, Investigation.

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Appendix

Supplementary Table 1
Follow-Up BPI-Pain Severity Improvement (or Reduction) scores from Baseline[a,b,c].

	Cryoneurolysis	Control
w1	0.99 (−0.64, 2.63)	0.32 (−1.14, 1.79)
w2	1.33 (−0.30, 2.96)	0.81 (−0.65, 2.27)
w3	1.79 (0.16, 3.42)	0.90 (−0.57, 2.36)
w4	2.02 (0.39, 3.65)	1.23 (−0.23, 2.70)
w5	2.18 (0.55, 3.81)	1.85 (0.39, 3.31)
w6	2.39 (0.76, 4.03)	1.81 (0.35, 3.27)
m2	2.73 (1.10, 4.36)	1.82 (0.36, 3.27)
m3	2.82 (1.18, 4.45)	2.27 (0.81, 3.73)
m4	3.25 (1.62, 4.89)	1.93 (0.45, 3.40)
m5	3.24 (1.60, 4.88)	2.38 (0.90, 3.87)
m6	3.10 (1.45, 4.74)	1.89 (0.41, 3.38)
Overall	2.35 (0.73, 3.97)	1.57 (0.13, 3.01)

BPI, brief pain inventory; PCS, pain catastrophizing scale; KL, Kellgren-Lawrence; BMI, body mass index; ASA, American Society of Anesthesiologists.
[a] Least square mean (LSM) and 95% confidence interval (CI) for pain severity improvement, which is calculated by: (baseline pain score − follow-up pain score). Positive values indicate pain improvement (or reduction) from the baseline, negative values indicate the opposite.
[b] Pain severity improvement was adjusted by PCS, KL grade, age, sex, BMI and ASA.
[c] Positive values in 95% CI indicate significant pain severity improvement ($P < .05$).

Supplementary Table 2
Follow-Up Functional Improvement Scores from Baseline[a,b,c].

	Cryoneurolysis	Control
w1	2.85 (−7.14, 12.85)	0.56 (−8.46, 9.58)
w2	8.58 (−1.41, 18.57)	5.15 (−3.83, 14.12)
w3	11.93 (1.93, 21.93)	7.85 (−1.15, 16.86)
w4	13.66 (3.67, 23.65)	9.46 (0.45, 18.47)
w5	14.40 (4.42, 24.39)	12.53 (3.55, 21.51)
w6	16.28 (6.25, 26.30)	13.34 (4.36, 22.33)
m2	18.72 (8.73, 28.70)	15.63 (6.67, 24.59)
m3	20.98 (10.97, 30.99)	20.50 (11.52, 29.48)
m4	25.71 (15.67, 35.75)	20.31 (11.21, 29.41)
m5	26.00 (15.92, 36.09)	22.48 (13.29, 31.67)
m6	25.40 (15.28, 35.53)	22.12 (12.91, 31.32)
Overall	16.77 (6.88, 26.67)	13.63 (4.84, 22.41)

PCS, pain catastrophizing scale; KL, Kellgren-Lawrence; BMI, body mass index; ASA, American Society of Anesthesiologists.
[a] Least square mean (LSM) and 95% confidence interval (CI) for functional improvement, which is calculated by: (follow-up functional score − baseline functional score). Positive values indicate functional improvement from the baseline, negative values indicate the opposite.
[b] Functional improvement was adjusted by PCS, KL grade, age, sex, BMI and ASA.
[c] Positive values in 95% CI indicate significant functional improvement ($P < .05$).

Supplementary Table 3
Follow-Up SD Improvement (or Reduction) scores from Baseline[a,b,c].

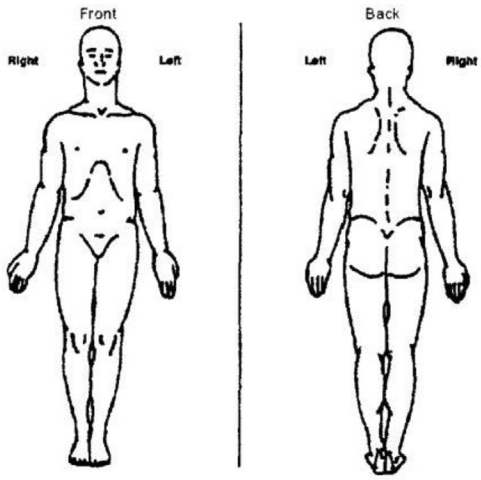
	Cryoneurolysis	Control
w1	3.74 (−1.66, 9.13)	1.44 (−3.45, 6.34)
w2	2.10 (−3.28, 7.49)	2.89 (−1.98, 7.75)
w3	3.75 (−1.65, 9.15)	1.60 (−3.30, 6.49)
w4	4.88 (−0.51, 10.27)	1.89 (−3.01, 6.78)
w5	5.62 (0.23, 11.00)	1.95 (−2.92, 6.82)
w6	6.89 (1.47, 12.30)	3.41 (−1.46, 8.28)
m2	7.10 (1.72, 12.49)	4.27 (−0.58, 9.12)
m3	8.38 (2.98, 13.78)	8.32 (3.45, 13.19)
m4	10.35 (4.93, 15.78)	6.93 (1.97, 11.89)
m5	8.94 (3.48, 14.39)	7.52 (2.49, 12.55)
m6	11.16 (5.67, 16.65)	8.42 (3.38, 13.46)
Overall	6.63 (1.34, 11.92)	4.42 (−0.27, 9.12)

PCS, pain catastrophizing scale; KL, Kellgren-Lawrence; BMI, body mass index; ASA, American Society of Anesthesiologists.
[a] Least square mean (LSM) and 95% confidence interval (CI) for SD improvement, which is calculated by: (baseline SD score − follow-up SD score). Positive values indicate SD improvement (or reduction) from the baseline, negative values indicate the opposite.
[b] SD improvement was adjusted by PCS, KL grade, age, sex, BMI, and ASA.
[c] Positive values in 95% CI indicate significant SD improvement ($P < .05$).

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain during the last week?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its ***worst*** in the last week.

0	1	2	3	4	5	6	7	8	9	10
No Pain									Pain as bad as you can imagine	

4. Please rate your pain by circling the one number that best describes your pain at its ***least*** in the last week.

0	1	2	3	4	5	6	7	8	9	10
No Pain									Pain as bad as you can imagine	

5. Please rate your pain by circling the one number that best describes your pain on the ***average***.

0	1	2	3	4	5	6	7	8	9	10
No Pain									Pain as bad as you can imagine	

6. Please rate your pain by circling the one number that tells how much pain you have ***right now***.

0	1	2	3	4	5	6	7	8	9	10
No Pain									Pain as bad as you can imagine	

7.What treatments or medications are you receiving for your pain?

Supplementary Figure 1. Brief Pain Inventory (Short-Form) Click or tap here to enter text.

8. In the last week, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much ***relief*** *you* have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how much, during the past week, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Scoring:

Pain Severity Score = Mean of items 3-6 (pain at its worst, pain at its least, average Pain Interference Score = Mean of items 9A-9G (interference of pain with: general activity, mood, walking, normal work, relations, sleep, enjoyment of life)

Supplementary Figure 1. (*continued*).