Diagnosis of Central Sensitization and Its Effects on Postoperative Outcomes Following Total Knee Arthroplasty: A Systematic Review and Meta-Analysis

Kim MS, Choi KY, Kwak DH, Cho RK, Jang HJ, Yang SC, In Y

Seoul St. Mary's Hospital
The Catholic University of Korea

Conflict of interest

Kim MS, MD. Ph.D.
Choi KY, MD.
Kwak DH, MD.
Cho RK, MD.
Jang HJ, MD.
Yang SC, MD.
In Y, MD, Ph.D.

We have no financial conflict to disclose.

Introduction

- Determining the cause of persistent pain after total knee arthroplasty (TKA) is important for those patients
- Despite the absence of abnormal findings in terms of surgical factors and having a physically well-functioning knee, some patients report persistent pain after surgery.
- Centralized pain is increasingly being considered a basis for pain patterns that cannot be explained by peripheral pain mechanisms. Cases of chronic pain without clear nociceptive input and specific tissue damage can be regarded as central sensitization (CS)
- CS can be defined as an amplification of neural signals within the CNS that causes pain hypersensitivity

Purpose

- **To investigate the diagnosis of CS in patients who underwent TKA for knee OA and discern the effect of CS on clinical outcomes after TKA. Moreover, if possible, we hoped to conduct a meta-analysis of the effects of CS on the clinical outcomes of TKA.**

Materials and Methods

- Multiple comprehensive databases: MEDLINE, EMBASE, and the Cochrane Library
- Search terms included (MeSH term “osteoarthritis” and key words “arthritis,” “osteoarthritis,” “osteoarthrosis,” “gonarthrosis,” and “gonoarthritis”) or (MeSH term “arthroplasty” and key words “replacement,” “joint replacement,” and “alloarthroplasty”), and (MeSH term “central nervous system sensitization” and key words “central sensitization,” “chronic pain,” “nociplastic pain,” and “widespread pain”).

Materials and Methods

- Two reviewers independently extracted data from each study using a standardized data extraction form
- Two reviewers independently assessed the methodological quality of each study using the Newcastle–Ottawa scale recommended by the Cochrane Non-randomized Studies Methods Working Group
- The outcomes (WOMAC, pain VAS score) were calculated and presented as standardized mean differences (SMDs) with 95% confidence intervals (CIs)

Results

	Country	Design	Age (Years)	Number of Patients (Proportion of Female Patients)	Study Length	Study Population
Sasaki et al. 2022	Japan	Prospective observation study	71.5	40 (85.0%)	3 months	Improved group with CS Remained group with CS
Kim et al. 2021	Korea	Retrospective study	CS: 69.4 Non-CS:70	CS: 102 (86.3%) Non-CS: 320 (89.4%)	24 months	CS Non-CS
Lape et al. 2020	Korea	Prospective observation study	66.1 (8.5)	176 (63.6%)	12 months	Widespread pain groups (Painful body regions 0 vs. 1–2 vs. ≥3)
Koh et al. 2020	Korea	Retrospective study	70 (57–83)	Total 222 (91%) CS: 55 (91%) Non-CS:167 (90%)	24 months	CS Non-CS
Dave et al. 2017	USA	Prospective observation study	Pain site 0: 66.5 Pain sites 1–2: 65.6 Pain sites ≥ 3: 67.2	Pain site 0: 53 (64.1%) Pain sites 1–2: 121 (55.4%) Pain sites ≥ 3: 67 (67.2%)	12 months	Widespread pain groups (Painful body regions 0 vs. 1–2 vs. ≥ 3) Subgroup analysis compared the group with ≥3 painful body regions and the group with 0 painful body regions.
Waldy et al. 2015	England	Additional study using RCT data		239 (52.3%)	12 months	Patients who underwent TKA to measure widespread pain sensitivity through QST
Kim et al. 2015	Korea	Prospective observation study	CS: 69.2 Non-CS: 71.1	94 (100%)	3 months	CS Non-CS
Waldy et al. 2013	England	Prospective cohort (exploratory study)	68	51 (56.9%)	13 months	Knee OA patients with QST Healthy people without knee pain Comparison of lower QST group and higher QST group in patients with knee OA pain by subgroup analysis

Results

Study	Proportion of CS at Baseline	Measure of CS	Postoperative Outcome Measure	Important Results and Comments
Sasaki et al. 2022	19(47.5%)	CSI	KOOS EQ-5D	Preoperative CS was negatively associated with EQ-5D score after TKA (β = −0.44, p = 0.017) Patients who maintained CS before and after surgery had inferior KOOS/EQ-5D results compared to those who improved (all p < 0.05)
Kim et al. 2021	102 (24.2%)	CSI	WOMAC	The CS group showed significantly inferior preoperative and postoperative WOMAC pain, function, and total scores compared to the no n-CS group (all p < 0.05) Preoperative WOMAC total score: CS 61.0 vs. non-CS 57.1 (p < 0.05) Postoperative WOMAC total score: CS 25.8 vs. non-CS 17.4 (p < 0.05) Preoperative WOMAC total score: CS 13.6 vs. non-CS 11.9 (p < 0.05) Postoperative WOMAC total score: CS 5.7 vs. non-CS 2.7 (p < 0.05)
Lape et al. 2020		Whole-body pain diagra m (19 sites labeled on th e diagram)	WOMAC	There was no significant association between changes in the widespread pain groups and changes in WOMAC pain scores (p > 0.05).
Koh et al. 2020	55 (24.8%)	CSI	Pain VAS WOMAC KSS Satisfaction (new KS S)	The CS group showed worse quality of life, functional disability, and dissatisfact-ion than the non-CS group after TKA (all p < 0.05). Postoperative pain VAS score: CS 2.3 vs. non-CS 1.0 (p < 0.05) Postoperative WOMAC total score: CS 25.2 vs. non-CS 15.4 (p < 0.05) Postoperative KSS total score: CS 165.3 vs. non-CS 177.6 (p < 0.05)
Dave et al. 2017		Whole-body pain diagra m (19 sites labeled on th e diagram)	WOMAC MCID	Preoperative widespread pain was associated with greater pain at 12 months and failure to reach the MCID (All p < 0.05) Patients with preoperative pain in 3–6 body regions showed higher WOMAC scores at follow-up compared to patients with no painful body regions (median, 10 vs. 0) and were also less likely to achieve MCID (77 % vs. 98%) (all p < 0.05)
Waldy et al. 2015		QST (PPT)	WOMAC VAS	There was no definite association between preoperative PPTs and pain severity at 12 months after TKA in any of the linear regression models (All p < 0.05)
Kim et al. 2015	44(46.8%)	CSI	Satisfaction (pain reli ef, functional improv ement)	Postoperative pain VAS score: CS 4 vs. non-CS 2 (p < 0.05) CS patients reported poor satisfaction regarding pain relief compared to non-CS patients (p < 0.05)
Waldy et al. 2013		QST (PPT and HPT)	WOMAC	When patients were divided into low and high preoperative forearm PPT groups, patients in the low PPT group showed worse 1-year W OMAC pain scores compa-red to patients in the high PPT group (85 vs. 95, p < 0.05)

Results

Quality Assessment of the Studies by the Newcastle–Ottawa Scale

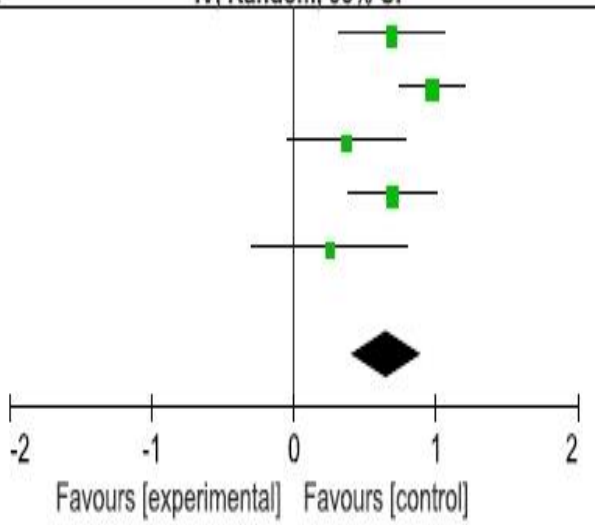
	Selection				Comparability		Outcome			
Study	Representative of the Cases	Selection of Control	Ascertainment of Exposure	Outcome of Interest Not Present at the Start of the Study	Comparability of Cohorts	Control for Any Additional Factor	Assessment of Outcomes	Sufficient Follow-Up	Adequacy of Follow-Up	Total 9/9
Sasaki et al. 2022	*	0	*	*	0	0	*	*	0	5
Kim et al. 2021	*	*	*	*	*	0	*	*	0	7
Lape et al. 2020	*	0	*	*	0	0	0	*	*	5
Koh et al. 2020	*	*	*	*	*	0	*	*	0	7
Dave et al. 2017	*	*	*	*	*	*	*	*	*	9
Waldy et al. 2015	*	0	*	*	0	0	*	*	0	5
Kim et al. 2015	*	*	*	*	*	*	*	*	*	9
Waldy et al. 2013	*	0	*	*	*	0	*	*	*	7

Results

Study or Subgroup	CS Mean	CS SD	CS Total	Non-CS Mean	Non-CS SD	Non-CS Total	Weight	Std. Mean Difference IV, Random, 95% CI
Dave et al 2017 [31]	11.67	18.95	66	1.67	3.81	51	19.6%	0.69 [0.31, 1.06]
kim et al 2015 [32]	5.7	3.6	102	2.7	2.9	320	26.8%	0.97 [0.74, 1.20]
Kim et al 2021 [29]	4	3.2892	44	2	6.8117	47	17.9%	0.37 [-0.05, 0.78]
Koh et al 2020 [30]	2.3	2.5	55	1	1.6	167	22.7%	0.70 [0.38, 1.01]
Waldy et al 2013 [35]	15	49.5161	26	5	24.226	25	13.1%	0.25 [-0.30, 0.80]
Total (95% CI)			**293**			**610**	**100.0%**	**0.65 [0.40, 0.90]**

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 10.08$, df = 4 (P = 0.04); $I^2 = 60\%$

Test for overall effect: Z = 5.04 (P < 0.00001)



- The pooled analysis showed that patients with CS have more severe postoperative pain after TKA (SMD, 0.65; 95% CI, 0.40–0.90; $p < 0.01$) with moderate heterogeneity ($I^2 = 60\%$)

Conclusion

- **In patients who underwent TKA with knee OA, CSI is most often used for screening CS, and QST and pain diagrams are also used.**
- **CS is closely associated with more severe and persistent pain after TKA.**
- **Based on reviews, when performing TKA in CS patients, it is important to develop realistic patient expectations through appropriate education on general postoperative pain patterns in CS.**

Reference

1. Woolf, C.J. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011, *152*, S2-s15.

2. Nijs, J.; Leysen, L.; Vanlauwe, J.; Logghe, T.; Ickmans, K.; Polli, A.; Malfliet, A.; Coppieters, I.; Huysmans, E. Treatment of central sensitization in patients with chronic pain: time for change? *Expert Opin Pharmacother* 2019, *20*, 1961-1970.

3. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009, *6*, e1000097.

4. Carbajal Mejía, J.B.; Wakabayashi, K.; Nakano, T.; Yatani, H. Marginal Bone Loss Around Dental Implants Inserted with Static Computer Assistance in Healed Sites: A Systematic Review and Meta-analysis. *Int J Oral Maxillofac Implants* 2016, *31*, 761-775.

5.Kim, M.S.; Koh, I.J.; Choi, K.Y.; Seo, J.Y.; In, Y. Minimal Clinically Important Differences for Patient-Reported Outcomes After TKA Depend on Central Sensitization. *J Bone Joint Surg Am* 2021, *103*, 1374-1382.

6.Koh, I.J.; Kang, B.M.; Kim, M.S.; Choi, K.Y.; Sohn, S.; In, Y. How Does Preoperative Central Sensitization Affect Quality of Life Following Total Knee Arthroplasty? *J Arthroplasty* 2020, *35*, 2044-2049.

7.Dave, A.J.; Selzer, F.; Losina, E.; Usiskin, I.; Collins, J.E.; Lee, Y.C.; Band, P.; Dalury, D.F.; Iorio, R.; Kindsfater, K., et al. The association of pre-operative body pain diagram scores with pain outcomes following total knee arthroplasty. *Osteoarthritis Cartilage* 2017, *25*, 667-675.

8.Kim, S.H.; Yoon, K.B.; Yoon, D.M.; Yoo, J.H.; Ahn, K.R. Influence of Centrally Mediated Symptoms on Postoperative Pain in Osteoarthritis Patients Undergoing Total Knee Arthroplasty: A Prospective Observational Evaluation. *Pain Pract* 2015, *15*, E46-53.