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Risk factors of chronic pain after total knee arthroplasty: a meta-analysis

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Abstract: *We systematically searched the Cochrane Library, EMbase, PubMed, Web of Science, China Journal Full-text Database (CNKI), Wanfang Digital Journal Full-text Database (Wanfang) and VIP journal Resource integration Service platform (VIP) database for published literature studies on the risk factors for chronic post-surgical pain (CPSP) in total knee arthroplasty (TKA) patients. The search period is up to March 10, 2023. Literature screening and data extraction were conducted independently by two researchers according to inclusion and exclusion criteria. After quality evaluation, meta-analysis was performed using Review Manager 5.3 software. Finally, 17 literatures were included. The results of meta-analysis showed that female [OR=1.32,95% CI(1.18,1.48),P<0.001], preoperative pain [OR= 1.76,95%CI(1.54,2.01),P<0.001], extensive pain[OR=3.11,95%CI(2.07,4.68),P<0.001], preoperative anxiety (OR = 2.80, 95% CI (0.83, 17.30), P < 0.001), preoperative depression (OR = 1.15, 95% CI (1.33, 5.87), P = 0.003] were TKA patients CPSP risk factors. Therefore, Clinical staff should identify and intervene in patients with high risk of CPSP after TKA as early as possible to reduce its incidence.*

Keywords: *Total knee arthroplasty; Chronic postoperative pain; Risk factors; Meta-analysis; Evidence-based nursing*

1. Introduction

Total knee anthroplasty (TKA) is a common clinical operation for the treatment of advanced knee diseases. It can improve joint function, correct joint deformity and relieve joint pain by replacing the damaged articular cartilage with artificial prosthesis. However, 10% to 35% of TKA patients experience chronic pain after surgery[1].Chronic post-surgical pain (CPSP) is defined as pain that persists for more than 3 months after surgery, excluding causes such as infection, surgical failure, and recurrence of malignant tumor[2].Long-term CPSP not only affects postoperative rehabilitation exercise, but also leads to patients' anxiety, depression, disappointment in surgical treatment and other negative emotions, increasing the contradiction between doctors and patients[3].Therefore, it is necessary to identify its influencing factors and formulate relevant intervention measures at an early stage.At present, studies on the influencing factors of chronic pain after total knee replacement have reached different conclusions due to different study populations, study regions and research tools. Moreover, meta-analyses on the influencing factors of chronic pain after total knee replacement have not been retrieved in China.Therefore, this study conducted a meta-analysis on the risk factors of chronic pain after total knee replacement, in order to provide a scientific basis for early clinical prevention and intervention.

2. Data and methods

2.1 Inclusion and exclusion criteria

2.1.1 Inclusion criteria

(1) Study population: age ≥18 years old, receiving TKA surgery; (2) Study content: Risk factors for CPSP in TKA: (3) Study type: case-control study, cohort study or cross-sectional study, search language was Chinese and English;

2.1.2 Exclusion criteria

(1) Meeting abstract, grey literature and other informal publication documents; (2) Review, review, animal experiments and republication of literature; (3) The full text cannot be obtained; (4) non-Chinese and English literature; (5) Low quality literature;

2.2 Search strategy

A computer search was conducted for studies on the influencing factors of chronic pain after total knee replacement from CNKI, VIP, China Biomedical Database, Wanfang, Pub Med, Web of Science, EMbase and Cochrane Library databases from inception to March 3, 2023. The retrieval strategies were (" total knee replacement "OR" artificial knee replacement "OR" total knee arthroplasty "OR" total knee arthroplasty ") AND (" chronic postoperative pain "OR" chronic postoperative pain "OR" persistent postoperative pain ") AND (" risk factors "OR "Influencing factor" OR "correlation" OR "prediction"), using a combination of subject words and free words.

2.3 Literature screening and data extraction

Two researchers read the titles and abstracts, eliminated duplicate references and apparently irrelevant references, and read the full text of references that might meet the inclusion criteria. The results in dispute shall be decided by both parties through consultation, and the opinion of the third researcher shall be consulted if necessary. After literature selection, data were extracted, including author, publication year, study type, sample size, influencing factors, etc

2.4 Literature quality evaluation

The Newcastle-Ottawa Scale (NOS) was used to evaluate cohort studies and case-control studies [4], which included 8 items in 3 categories: selection of study population, comparability between groups, and exposure factors, with a full score of 9. The score 0-3 was classified as low-quality studies. A score of 4-6 is considered to be of medium quality, and a score of 7-9 is considered to be of high quality. The cross-sectional study used the evaluation criteria recommended by U.S. health care quality and research institutions[5]. Literature quality was independently evaluated by two researchers, and the higher the score, the higher the quality of the literature.

2.5 Statistical Methods

A meta-analysis of the included literature was performed using Rev Man 5.3 software. If the heterogeneity test $P \geq 0.1$ and $I2 \leq 50\%$, indicating homogeneity between studies, the fixed-effect model was used for combined analysis. If $P<0.1$ and $I2>50\%$ indicate heterogeneity among studies, sensitivity analysis or subgroup analysis should be used to find the source of heterogeneity. If heterogeneity is still large, random-effects model should be used or results combining should be abandoned. When there were more than 10 literatures included in the single risk factor analysis, funnel plot was used to analyze the publication bias of each risk factor. $P<0.05$ indicated that the difference was statistically significant.

3. Results

3.1 Literature search, the basic characteristics and quality evaluation results of the included literatures

A total of 395 literatures were obtained by searching the database, and 309 literatures were obtained by removing duplicate literatures. After preliminary reading of the title and abstract of the literatures, and excluding reviews, systematic reviews and irrelevant literatures, 48 literatures remained. After reading the full text, 6 literatures were further excluded, 2 outcomes were inconsistent, and 24 literatures could not provide complete data. Finally, 17 literatures [6-22] were included. Among them, there were 11 case-control studies, 5 cohort studies and 1 cross-sectional investigation, with a sample size of 3575 cases. The basic characteristics of the included literatures are shown in Table 1.

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Table 1: Basic characteristics and methodological quality evaluation results of included literatures

Included study	Publication year (year)	Nation	Study type	Sample size	Literature quality evaluation	Risk factors
Guoli Wan et al	2023	China	Case-control study	212	8[1)]	1,5,6,7,8
Hardy et al	2022	France	Case-control study	103	9[1)]	1,2,3,4
Hasegawa et al	2022	Japan	Case-control study	58	6[1)]	2
Jieru Chen et al	2022	China	Cohort study	240	9[1)]	2,9
Dandan Longet al	2022	China	Case-control study	200	9[1)]	3,10,11,12
Haiping Luo et al	2022	China	Case-control study	185	9[1)]	3,13,14,15,16
Koji et al	2021	Japan	Cohort study	194	9[1)]	1,17
Fan Chen et al	2021	China	Case-control study	120	7[1)]	18,19
Wanlan Ding et al	2021	China	Case-control study	160	8[1)]	3,20,21,22,23
Jinjun Zhang et al	2021	China	Case-control study	338	9[1)]	1,24,25,26
Semih et al	2019	America	Cohort study	578	9[1)]	1,27,28
Peter et al	2019	Denmark	Cohort study	352	7[1)]	1,10,29,30,31
Joséphine et al	2016	France	Case-control study	104	8[1)]	33,34,35
Nadine et al	2014	France	Cohort study	89	9[1)]	3
Christophe et al	2014	France	Case-control study	69	8[1)]	36
Liu et al	2012	America	Cross-sectional study	251	8[2)]	10,12,37,38
Pia et al	2010	Denmark	Case-control study	562	8[1)]	12

Note: 1.the visual analog score of preoperative pain;2.Preoperative pain catastrophizing;3 preoperative anxiety and depression;4.Preoperative pain for at least 3 years;5.sleep;6. hip, knee and ankle Angle 7.visual analog score of pain at discharge;8.the use time of blood tape;9 Use NSAIDs within 6 months;10.indicates the presence of widespread pain;11.preoperative central sensitization;12.female; 13.acute pain 24h after surgery.14.preoperative coping mode to avoid pain;15.the brave face of pain coping in the 3 months after surgery;16.knee function score 3 months after operation;17.the postoperative coronal plane is not aligned;18.the plasma AT2R concentration before operation;19.Preoperative paindetect self-evaluation scale score;20.infection;21.the standard for the use of tourniquet;22.lower extremity venous thrombosis;23.effectively carry out functional exercise; 24.Low C-reactive protein level after operation;25.Postoperative knee joint swelling;26.the low effective compression rate of self-controlled analgesia pump;27.race;28.different anesthesia methods; 29.fibromyalgia;30.previous cancer diagnosis;31unstable knee joint;32.the youngest age;33.low educational background;34.lack of physical activity;35.the effect of pain on walking ability; 36.postoperative pain;37.the history of previous knee surgery. 1) Newcastle-Ottawa scale; 2) Methodological checklist for national health care quality and research institutions.

3.2 Results of meta-analysis

3.2.1 Gender

Three studies [8, 21, 22] reported the influence of gender on postoperative CPSP in TKA patients, and there was no heterogeneity among the study results (I^2=38%,P=0.20). Combined analysis with fixed effect model showed that females were the influencing factor for postoperative CPSP in TKA patients. The difference was statistically significant [OR=1.32, 95%CI(1.18,1.48),P<0.001].

3.2.2 Preoperative pain

Six studies [6, 10, 13, 15-17] reported that preoperative pain was associated with postoperative CPSP in TKA patients, and there was a large heterogeneity among the studies (I2=67%,P=0.009). Sensitivity analysis found that Koji's study was the source of heterogeneity. Heterogeneity among other studies was acceptable after exclusion (I^2=42%,P=0.14). The fixed-effect model was used for meta-analysis, and the results showed that preoperative pain was a risk factor for postoperative CPSP in TKA patients, with statistical significance [OR=1.76,95%CI(1.54,2.01),P<0.001].

3.2.3 Preoperative pain catastrophizing

Three studies [9, 13, 14] reported the effect of preoperative pain catastrophizing on postoperative CPSP

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in TKA patients, and there was no heterogeneity among the study results (I^2=11%,P=0.33). Combined analysis using the fixed-effect model concluded that pain catastrophizing was an influential factor in postoperative CPSP in TKA patients. The difference was statistically significant [OR=3.11,95%CI(2.07,4.68),P<0.001].

3.2.4 Widespread pain

Three studies [8, 17, 22] reported that widespread pain was associated with postoperative CPSP in TKA patients, with high heterogeneity (I^2=85%,P=0.001). Sensitivity analysis found that Long Dadan's study was the source of heterogeneity, and heterogeneity among other studies was acceptable after exclusion (I^2=40%,P=0.20). A meta-analysis using a fixed-effect model showed that widespread pain was a risk factor for postoperative CPSP in TKA patients, and the difference was statistically significant [OR=2.12,95%CI(1.75,2.57),P<0.001].

3.2.5 Preoperative anxiety and depression

Five studies [7, 8, 11, 13, 19] reported that preoperative anxiety and depression were associated with postoperative CPSP in TKA patients, and the data of three studies [11, 13, 19] on preoperative anxiety could be combined for analysis. The heterogeneity of the studies was large (I2=78%,P=0.01). The sensitivity analysis found that, Nadine's study was the source of heterogeneity, and the heterogeneity among other studies was acceptable after exclusion (I2=42%,P=0.19). The fixed effect model was used for meta-analysis, and the results showed that preoperative anxiety was a risk factor for postoperative CPSP in TKA patients. The difference was statistically significant [OR=2.80, 95%CI(0.83,17.30), P<0.001].

The data of three [7, 11, 19] studies on preoperative depression could be combined for analysis, and the heterogeneity of each study was high (I2=65%,P=0.06). Sensitivity analysis found that Wanlan's study was the source of heterogeneity, and the heterogeneity among other studies was acceptable after exclusion (I2=0%,P=0.38). The fixed effect model was used for meta-analysis, and the results showed that depression was a risk factor for postoperative CPSP in TKA patients, with statistical significance [OR=1.15,95%CI(1.33,5.87),P=0.003].

3.3 Sensitivity analysis

The sensitivity analysis of the combined risk factors in this study was carried out using the results of fixed effect model and random effect model respectively, and the results showed that the combined effect sizes were close, suggesting that the results of this study were stable. See Table 2.

Table 2: Sensitivity analysis results [OR(95%CI)]

factor	Fixed effect model	Random effects model
Gender	1.32 [1.18, 1.48]	1.35 [1.15, 1.60]
Preoperative pain	1.76 [1.54, 2.01]	1.86 [1.51, 2.29]
Preoperative pain catastrophizing	3.11 [2.07, 4.68]	3.15 [2.01, 4.94]
widespread pain	2.12 [1.75, 2.57]	2.67 [1.05, 6.74]
Preoperative anxiety	2.80 [1.33, 5.87]	3.79 [0.83, 17.30]
Preoperative depression	1.15 [1.05, 1.26]	1.15 [1.05, 1.26]

3.4 Publication bias analysis

In this study, less than 10 literatures were included for a single influencing factor, so funnel plot analysis was not conducted.

4. Discussion

4.1 Gender

The meta-analysis showed that the risk of CPSP after TKA was 1.32 times higher in women than in men. It may be due to the fact that compared with men, women have lower postoperative sensory thresholds and pain thresholds and are more sensitive to pain perception [23]. Secondly, studies [24, 25] show that gender leads to differences in CPSP after TKA surgery, which may also be related to the influence of biological and psychosocial factors. Women are more abundant in psychological emotions, more prone to depression, and further increase the experience of pain. At the same time, women may be more inclined to deal with pain through interpersonal communication. Actively and quickly report and act on pain. It is suggested that nursing staff should pay more attention to the female patients with CPSP after TKA, and conduct psychological nursing intervention in time to reduce the occurrence of pain.

4.2 Preoperative pain and widespread pain

Results of meta-analysis showed that the risk of CPSP in patients with moderate and severe preoperative pain was 1.76 times higher than that in patients with low-intensity preoperative pain. It may be that the higher the degree of pain, the more likely it is to lead to the sensitization of nociceptors and neurons of the central nervous system, and the continuous introduction of preoperative painful stimulation to the central nervous system is easy to cause central nervous remodeling, and then the occurrence of postoperative CPSP [26]. It is suggested that medical staff should pay attention to the evaluation of patients' pain before operation, and make good management of pain to reduce the occurrence of postoperative CPSP. Widespread pain is pain in other parts of the body besides the surgical site. The risk of CPSP in patients with widespread pain was 2.21 times higher than that without widespread pain. Studies have shown [8] that the potential mechanism of chronic pain caused by widespread pain may be related to peripheral nerve sensitization, central nerve sensitization, and abnormal descending pathway. Therefore, medical workers should pay attention to identifying such patients and do a good job in perioperative pain management of patients.

4.3 Preoperative pain catastrophizing

Pain catastrophization has been defined as "an exaggerated negative mental stereotype of experiencing actual or anticipated pain", consisting mainly of rumination (ruminating on the pain experience), exaggeration (amplifying the threat of pain), and helplessness (feeling unable to cope with pain) [27]. The results of this study showed that patients who experienced pain catastrophizing before TKA were 3.11 times more likely to develop CPSP after surgery than those who did not. It is possible that patients will pay too much attention to pain symptoms, fear pain, and feel that they are unable to cope with pain, so they take avoidance strategies, reduce their activity, and aggravate the experience of pain. The central nervous system of pain may become more sensitive, resulting in chronic hyperalgesia, which further leads to the occurrence of postoperative CPSP [28, 29]. It is suggested that the medical care should pay attention to the evaluation of the disaster of pain before operation, formulate the intervention measures of psychological nursing, reduce the risk of chronic pain, and make patients benefit.

4.4 Preoperative anxiety and depression

The results of meta-analysis showed that the risk of CPSP in patients with anxiety before TKA was 2.08 times higher than that in patients without anxiety. Patients who were depressed before TKA had a 1.15 times greater risk of developing CPSP after surgery than those who were not depressed.

It may be due to the fact that negative emotions can activate certain substances in the hypothalamus, enhance patients' perception of pain and amplify their feelings of pain, and the interaction between chronic pain and depression, both of which can cause changes in brain structure and function, and lead to vicious cycles if not managed [30, 31]. Therefore, medical personnel should pay attention to the management of anxiety, depression and chronic pain in TKA patients. In addition to routine analgesia, anti-anxiety and depression medication, such patients should also be psychologically counseling to reduce the adverse consequences caused by their mutual influence.

5. Summary

The results of this study showed that female, preoperative pain, widespread pain, preoperative pain catastrophizing, preoperative anxiety and depression were risk factors for postoperative CPSP in TKA patients. In order to reduce the incidence of postoperative CPSP in TKA patients, medical staff should evaluate high-risk groups in a timely manner based on risk factors and formulate personalized interventions. In addition, there are some limitations in this study, including only Chinese and English literature, which may have publication bias. Differences in sample size, institutions, exposure factors, medical environment, and economic level among the included literatures led to high heterogeneity in

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some of the findings. Most of the included studies were small sample, single-center case-control studies. Therefore, large sample, multi-center, high-quality prospective cohort studies and randomized controlled studies should be conducted in the future to comprehensively and deeply explore the risk factors of postoperative CPSP in patients with TKA, and formulate corresponding intervention programs to provide a basis for the prevention and intervention of patients with chronic pain after TKA.

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