

INPLASY PROTOCOL

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Corresponding author:
Ambarish Dutta

ambarish.dutta@iiphb.org

Author Affiliation:
Additional Professor,
Epidemiology, Indian
Institute of Public Health-
Bhubaneswar, Pubic Health
Foundation of India.

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Conflicts of interest:
None declared.

Protocol for A systematic review of utility values of total knee replacement vs non-surgical management among 40 years and above population with knee osteoarthritis

Nanda, L¹; Dutta, A²; Rout, SK³; John, J⁴; Anilkumar, A⁵; Gandhi, N⁶; Dhopte, PR⁷; Qadeer, AS⁸.

Review question / Objective: Clinically, the knee is the most common site of OA, followed by the hand and hip. The basic research question of our study is: Among patients with osteoarthritis knee, aged 40 and above, is total knee replacement with post-surgical management associated with better functional outcomes and quality of life compared to non-surgical management? Based on this review question, the following objectives are proposed, 1. To identify “Markov states” and “Transition states” along with utility values for total knee replacement and non-surgical management. 2. To estimate the QoL difference of total knee replacement compared to non-surgical management. Population: Patient aged ≥ 40 years with Knee Osteoarthritis All Kellgren Lawrence grade. Intervention: Total Knee Replacement + Postsurgical Management Comparator: Non-Surgical Management – Acetaminophen, oral & topical NSAIDs, COX-2 inhibitors, Celecoxib, Rofecoxib, Valdecoxib, Opioids, Glucosamine sulphate, Dicerhein, Intra-articular steroid injections, physiotherapy, Yoga. Outcome: QoL gained.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 May 2021 and was last updated on 12 May 2021 (registration number INPLASY202150045).

INTRODUCTION

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patients with osteoarthritis knee, aged 40 and above, is total knee replacement with post-surgical management associated with better functional outcomes and quality of life compared to non-surgical

management? Based on this review question, the following objectives are proposed, 1. To identify “Markov states” and “Transition states” along with utility values for total knee replacement and non-surgical management. 2. To estimate the QoL difference of total knee replacement compared to non-surgical management. Population: Patient aged ≥ 40 years with Knee Osteoarthritis All Kellgren Lawrence grade. Intervention: Total Knee Replacement + Postsurgical Management Comparator: Non-Surgical Management – Acetaminophen, oral & topical NSAIDs, COX-2 inhibitors, Celecoxib, Rofecoxib, Valdecoxib, Opioids, Glucosamine sulphate, Diacerhein, Intra-articular steroid injections, physiotherapy, Yoga. Outcome: QoL gained.

Rationale: This Systematic review is being conducted as a part of the health technology assessment on estimating the clinical and cost effectiveness of TKR+ post-surgical management to non-surgical management. As India aims to achieve Universal Health Coverage, there is a need to ramp up its primary care infrastructure and also introduce public-funded health insurance and assurance schemes to finance healthcare. (PMJAY) being one of the insurance choices in the public exchange place, cost-effectiveness of important disability-alleviating procedures like TKA assumes extreme importance as this may help to allocate resources efficiently for such critical procedures within the ambit of insurance and address the issue of moral hazard effectively. With an increase in ageing population, new technological advancements, and competition for limited resources demand judicious resource allocation globally. In the present era, there are limited medical resources the healthcare provider must know the clinical and cost-effectiveness of the treatment. This is true for TKA as a seminal management procedure for the disabling condition that is knee OA, which is also on the rise across the globe. Therefore, it is imperative that a comprehensive health technology assessment is carried out for TKA in India, which becomes even more relevant given

the scarcity of this information in India. This systematic review attempts to establish the effectiveness of total knee replacement in terms of quality of life. This, along with the costing data is expected to provide evidence of the cost effectiveness of total knee replacement compared to non-surgical management for those with osteoarthritis knee. Attempts to extrapolate and generalize such cost-effectiveness information from the developed world for use in decision-making in India may not be prudent given the vast differences in costs and other related metrics between these two diverse cultures.

Condition being studied: Osteoarthritis (OA) is a chronic degenerative disease characterized by deterioration of the cartilage in joints, a leading cause of disability globally. The characteristics of the knee OA comprises muscle weakness, fatigue and increased pain in joints. These symptoms when progresses it will lead to decreased mobility, deconditioning, reduced functional capacity and mobility and overall contributes to decline in patient’s quality of life. Clinically, the knee is the most common site of OA, followed by the hand and hip. Osteoarthritis is the second most common rheumatologic problem and is the most recurrent joint disease encountered in the clinical practice in Indian and Asian populations aged 40 and above with a prevalence in the range of 22% to 39%. Knee osteoarthritis is considered to have an estimated prevalence of 3.8% radio-graphically confirmed symptomatic cases. The prevalence was found to be higher among females than in males and peaked at around 50 years of age. According to the Global Burden of Disease 2010 Study, only hip and knee OA, the most commonly affected joints by the disease condition, ranked 11th highest in terms of YLDs (lives lived with disability) and 38th highest in terms of overall disease burden calculated in terms of Disability Adjusted Life Years (DALYs) among 291 conditions. With the burden of OA being on the rise, osteoarthritis has significant implications on the individuals affected, the healthcare

system, and also broader socioeconomic repercussions on the society. Symptomatic knee osteoarthritis or gonarthrosis has been shown to have a significant impact on the quality of life (QoL) of the patients suffering from the condition. Health-related quality of life (HRQoL) is a multidimensional concept equipped to assess the impact of health status on areas related to the quality of life such as physical and psychosocial wellbeing, the fulfillment of life roles, and satisfaction, in contrast, to merely objective changes in health status. This metric is commonly used in clinical effectiveness and economic evaluation studies to determine how effective are treatments or how they relate to cost-effectiveness. Total knee arthroplasty (TKA) is proven to be extremely effective in treating symptoms of OA and is also associated with high patient satisfaction and improved QoL. Based on the Kellgren Lawrence grade, severity and pain of knee OA would be assessed and the patients with all KL grades will be considered for the study.

METHODS

Search strategy: The outcome measures included were Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Society Score (KSS), EQ5D, Visual Analytical Scale (VAS), Knee Injury, and Osteoarthritis Outcome Score (KOOS), SF 36/12, Quality of life (QoL). A literature search was performed on 20th November 2020 using the PubMed database by three authors (AA, PD, RS) and research articles published after 2010 were only included. The search term was formulated after conducting a thorough literature for relevant keyword identification. The MESH terms for keywords of interest were identified and Boolean operators were used in conjunction to prepare the search parameter. The final search parameters used were: ("Osteoarthritis, Knee"[Mesh]) AND (("Arthroplasty, Replacement, Knee"[Mesh]) AND ("Transcutaneous Electric Nerve Stimulation"[Mesh] OR "Transcutaneous Electric Nerve Stimulation"[Mesh] OR "Massage"[Mesh]

OR "Diphosphonates"[Mesh] OR "Glucosamine"[Mesh] OR "Methotrexate"[Mesh] OR "Tumor Necrosis Factor Inhibitors"[Mesh] OR "Platelet-Rich Plasma"[Mesh] OR "Chondroitin"[Mesh] OR "Hyaluronic Acid"[Mesh] OR "Botulinum Toxins"[Mesh] OR "Prolotherapy"[Mesh] OR "Colchicine"[Mesh] OR "Fish Oils"[Mesh] OR "Vitamin D"[Mesh] OR "Exercise"[Mesh] OR "Weight Loss"[Mesh] OR "Tai Ji"[Mesh] OR "Acupuncture"[Mesh] OR "Exercise Therapy"[Mesh] OR "Yoga"[Mesh] OR "Steroids"[Mesh] OR "Acetaminophen"[Mesh] OR "Tramadol"[Mesh] OR "Duloxetine Hydrochloride"[Mesh] OR "Capsaicin"[Mesh] OR "Weight Loss"[Mesh] OR "Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "Braces"[Mesh] OR "Therapeutic Irrigation"[Mesh] OR "Analgesics, Opioid"[Mesh] OR "Viscosupplementation/adverse effects"[Mesh] OR "Viscosupplementation/economics"[Mesh] OR "Viscosupplementation/methods"[Mesh] OR "Viscosupplementation/pharmacology"[Mesh] OR "Viscosupplementation/statistics and numerical data"[Mesh] OR "Viscosupplementation/therapeutic use"[Mesh] OR "Steroids"[Mesh])).

Participant or population: Patients whose age is above ≥ 40 years with knee Osteoarthritis with all Kellgren -Lawrence grades will be considered. According to the WHO report, the prevalence of osteoarthritis is higher among older adults aged 40 years and above. Both male and female with knee OA will be included. Studies suggested total knee replacement to be the treatment of choice among patients diagnosed with Kellgren Lawrence grade \geq III. However, in India moral hazard associated with TKR is high where patients with lower KL-grade OA are undergoing TKR. Hence, the review will include studies conducted on patients diagnosed with all Kellgren-Lawrence grades osteoarthritis knee.

Intervention: All approaches of Total knee arthroplasty (TKA) such as posterior

stabilizing, cruciate retaining & constraint approaches will be considered for the review. Total knee arthroplasty is extremely effective in treating symptoms of OA and is also associated with high patient satisfaction and improved QoL. TKA is performed to improve the patient's function, correct deformity, maintain balance in mobility and alleviate the knee pain. It is a proven effective means for relieving the pain and other symptoms associated with Knee OA. It is a common surgical modality practiced in western countries like Spain, Russia, UK, USA and Australia. Despite its effectiveness, financial and resource constraints prohibit its widespread use in developing countries like India. The review will exclude studies which assess bilateral total knee replacement and revision TKA.

Comparator: NHSRC report suggests non-surgical management as the primary choice of treatment for patients with osteoarthritis over any surgical treatments. The common non-surgical managements of choice for osteoarthritis knee include pharmacological and non-pharmacological measures. Pharmacological measures include analgesics, anti-inflammatory agents, visco-supplements such as hyaluronic acid, glycosaminoglycans and intra-articular injections of steroids. Non-pharmacological measures include physiotherapy, exercise and dietary management.

Study designs to be included: Reports of Randomized Control Studies (RCT), cohort studies, and cross-sectional studies will be included.

Eligibility criteria: Randomized control trial, quasi-randomized control trial considering TKR (+Postsurgical Management) and Non-surgical management, and prospective cohort study where pre-treatment and post-treatment effectiveness score is compared will be used for the review. Studies involving participants \geq 40 years of age will be included. The studies including both clinical effectiveness like KOOS (Knee Injury and Osteoarthritis Outcome Score), WOMAC (Western Ontario

and McMaster University Osteoarthritis Index), OKS (Oxford Knee Scores), Knee Society Score (KSS) and/or patient-reported utilities such as EQ5D (Euro QoL 5 dimensional); Visual Analog Scale (VAS), SF-12, SF-36 will be taken into consideration. Studies conducted from 2010 onwards will only be included for the review. Studies assessing total knee replacement performed for causes other than age-related osteoarthritis (e.g traumatic osteoarthritis) will be excluded from the review.

Information sources: An electronic search will be done to identify the relevant studies. The studies conducted on humans, those which are published in the English language will be considered for the exercise. The following electronic database will be used for the search of studies and the appropriate MeSH terms/search strategies will be employed. a. Cochrane Central Register of Controlled Trials (CENTRAL) b. NHS Database c. MEDLINE (PubMed) d. HTAIn repository.

Main outcome(s): The outcomes of interest assessed using the scoring systems from the inclusion criteria will be included. Hence, WOMAC, OKS, KSS, SF-12, SF-36 will be used. WOMAC measures the condition of patients with osteoarthritis knee in terms of pain, stiffness and function. OKS measures the outcomes of patients following total knee arthroplasty. Knee Society Score assesses the parameters such as pain and functional ability of patients with osteoarthritis knee. SF-12 and SF 36 measure the quality of life of those with chronic health conditions. KOOS measures the patients' perspective regarding their osteoarthritis knee and associated health problems. VAS is a generic measure for assessing the pain due to osteoarthritis knee and post-TKR. The outcomes of interest measured at baseline and at the end of 1 year will be used for the systematic review. The outcomes will be mapped to EQ5D which is a generic measure for quality of life. The change in EQ5D scores at the end of 1 year is expected to provide the improvement in functional outcomes due to total knee

replacement and non-surgical management.

Additional outcome(s): Nil.

Data management: The studies included in systematic review will be imported into COVIDENCE software. After primary and secondary screening, the studies to be included for systematic review will be finalized. The information collected will be summarized into a matrix created on MS-Excel. The matrix will include the study name, author name, objectives, population, inclusion, exclusion criteria, methodology, outcome estimation, measures of association, sensitivity analysis and study findings.

Quality assessment / Risk of bias analysis: A narrative synthesis will be performed initially with the included studies. Risk of bias will be assessed using Cochrane Risk of Bias tool (RoB). Studies with high-risk and unclear risk of bias will be excluded from the review.

Strategy of data synthesis: The effectiveness of Knee Osteoarthritis (both surgical and non-Surgical) management and quality of life (QoL) will be obtained from a systematic literature review. The extracted clinical effectiveness data will be converted into patient-reported utility score (EQ5D) by appropriate mapping method. Narrative synthesis will be done for the included studies on both total knee replacement and non-surgical management. The statistical analysis will be done with the help of a meta-analysis approach by implementing the subgroup method or meta-regression giving appropriate weightage to each study. The mean utility score will be calculated for intervention and comparator. The collected data will be entered in MS-Excel and analyzed using STATA 13 for Windows. The data will be summarized using tables and figures. Numerical data will be presented using tables with means or standard deviations or medians with interquartile ranges. Categorical data will be presented using percentages.

Subgroup analysis: Depending on feasibility, a subgroup analysis based on age group and severity group (based on Kellgren-Lawrence classification grades) will be conducted to ascertain the most optimum group for Total Knee Replacement (+Postsurgical Management).

Sensitivity analysis: The probabilistic sensitivity analysis will be conducted to address the issue of heterogeneity of patients. One-way sensitivity analysis will be done for estimating utility value.

Language: No language limits were imposed for selection of studies for the review.

Country(ies) involved: India.

Keywords: Cost utility analysis; Knee osteoarthritis; Total Knee replacement; non-surgical management; EQ5D; Markov Model; QALY.

Dissemination plans: The results of this study would be published in a peer-reviewed indexed journal. The findings from the systematic review would be communicated to the Department of Health Research as a part of the Health Technology Assessment Report on the cost-utility of total knee replacement for osteoarthritis knee patients.

Contributions of each author:

Author 1 - Lipika Nanda - The author contributed to the Conception and design, Acquisition of data, Analysis and interpretation of data, Systematic literature review, Data extraction, Drafting of the manuscript, Critical revision of the manuscript for important intellectual content, Statistical analysis, Administrative and technical support.
Email: lnanda@iipbh.org

Author 2 - Ambarish Dutta - The author contributed to the Conception and design, Acquisition of data, Analysis and interpretation of data, Systematic literature review, Data extraction, Drafting of the manuscript, Critical revision of the manuscript for important intellectual

content, Statistical analysis, Technical support.

Email: ambarish.dutta@iiphb.org

Author 3 - Sarit Kumar Rout - The author contributed to the Conception and design, Acquisition of data, Analysis and interpretation of data, Systematic literature review, Data extraction, Drafting of the manuscript, Critical revision of the manuscript for important intellectual content, Statistical analysis, Technical support.

Email: sarit.kumar@phfi.org

Author 4 - Jebamalar John - The author contributed to Conception and design, Acquisition of data, Analysis and interpretation of data, Systematic literature review, Data extraction, Drafting of the manuscript, Critical revision of the manuscript for important intellectual content, Statistical analysis, Technical support.

Email: jebamalar.j@iiphh.org

Author 5 - Aiswarya Anilkumar - The author contributed to the Conception and design, Acquisition of data, Analysis and interpretation of data, Systematic literature review, Data extraction, Drafting of the manuscript, Critical revision of the manuscript for important intellectual content, Statistical analysis, Technical support.

Email: aiswarya.anil@iiphh.org

Author 6 - Naline Gandhi - The author contributed to the Conception and design, Acquisition of data, Analysis and interpretation of data, Systematic literature review, Data extraction, Drafting of the manuscript, Critical revision of the manuscript for important intellectual content, Statistical analysis, Technical support.

Email: naline.g@iiphh.org

Author 7 - Pratik Ramesh Dhopte - The author contributed to the Conception and design, Acquisition of data, Analysis and interpretation of data, Systematic literature review, Drafting of the manuscript, Statistical analysis and Technical support.

Email: pratikramesh2016@gmail.com

Author 8 - Amatullah Sana Qadeer - The author contributed to the Conception and design, Acquisition of data, Analysis and

interpretation of data, Systematic literature review, Drafting of the manuscript.

Email: sana@iiphh.org