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REVIEW

Clinical Outcomes of Methotrexate Usage in Postoperative Arthroplasty Patients: An Evidence Based Review

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Abstract: Patient dissatisfaction after joint arthroplasty remains common. Synovitis is known to contribute to patient dissatisfaction in patients with osteoarthritis. Methotrexate (MTX) is commonly used to prevent joint deterioration in rheumatoid arthritis, however it is much less common in the treatment of osteoarthritic patients. This review explores the effect of MTX on surgical outcomes in the general arthroplasty patient population. While most of the papers reviewed include patients with rheumatoid arthritis, we also review papers that include patients with osteoarthritis and juvenile idiopathic arthritis. Publications were queried in PUBMED and OVID MEDLINE using the following terms: arthroplasty, joint replacement, methotrexate, DMARDs, osteoarthritis, rheumatoid arthritis, arthritis. After applying exclusion criteria, we identified 12 publications for this review. Our results showed no significant increase in revisions or long-term infections were reported in patients taking MTX. One study reported detriment to nerve function with postoperative MTX use. All other studies reported no difference in post-operative pain or function scores. One study investigating the effect of MTX on mobility in rheumatoid arthritis patients following arthroplasty showed improvement in function in patients taking MTX. Thus, based on this review, perioperative MTX use does not appear to worsen arthroplasty outcomes. This review should suffice as a building block for further investigations and trials into MTX's utility for arthroplasty patients.

Keywords: DMARD, osteoarthritis, rheumatoid arthritis, arthritis, joint replacement

Introduction

Arthroplasty outcomes and patient satisfaction vary depending on the type of arthroplasty. Notably knee arthroplasty can have up to a 19% dissatisfaction rate.[1] Many factors contribute to patient dissatisfaction, including infection, malalignment, and of particular interest here: synovitis.[2]

Synovitis is a common topic of discussion in inflammatory arthropathies like rheumatoid arthritis (RA). In this setting, corticosteroids and disease modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX) are used to treat the inflammation and reduce pain and symptoms. In the context of arthroplasty, MTX has been used in RA patients for several decades with notable effects on overall disease progression and evidence of prolongation of time to arthroplasty.[3]

Osteoarthritis (OA) is often spoken of as "wear and tear" arthritis, however there is a significant inflammatory component to OA as well. OA is often associated with synovitis as well as immune cell infiltration and high cytokine levels. In fact, worse synovitis has been associated with worse pain[4] and altered gait.[3] Given the significant effects of synovitis on pain and function in OA patients, some have asked whether OA-related inflammation could also be treated with MTX.[4] In a recent prospective randomized controlled trial, 155 patients were administered MTX or a placebo medication for 12 months. In this study, patients in the MTX group had significantly less pain and stiffness and improved function than those in the placebo group, suggesting that oral MTX reduces pain and improves function in patients with OA.[4] A subsequent metanalysis looking at 6 randomized controlled trials concluded that MTX was safe and effective in

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reducing pain and improving function in patients with knee OA.[5] Seeing that MTX has been shown to be helpful in the treatment of OA before arthroplasty, it remains to be seen if some post-arthroplasty causes of pain in OA patients could be addressed through MTX.

The use of both steroids and MTX in the perioperative setting has been studied mostly in the setting of RA. In RA, physicians need to balance the theoretical risk of immunosuppression with the need to obtain adequate perioperative symptom control. Within the RA population, patients who have an active RA flare within 6 weeks of total joint arthroplasty have worse pain and function scores at the 1 year post-op mark than those with controlled RA.[6] There is extensive evidence to suggest that continuous MTX use in the perioperative elective orthopaedic surgery setting has no effect on wound healing or infection rates.[7] The literature surrounding steroid use in the perioperative setting is less clear, however there does not appear to be good evidence to support stopping steroids perioperatively.[8] This is reinforced by a study by Ren et al suggesting that patients receiving DMARDs and glucocorticoid agents to control their symptoms in the perioperative period have better functional outcomes than those exclusively taking DMARDs or taking no RA medications at all in the perioperative period.[9] Given that perioperative symptom control is important and use of traditional RA treatment modalities like steroids and MTX do not increase complication rates, the available evidence would suggest that these agents should be continued in the perioperative setting.

So far, most of the available research around DMARD use perioperatively focuses on outcomes like wound healing and infection or RA flares. While these are important measures, there is a need for a review of the clinical outcomes such as functional and pain scores associated with MTX in the generalized arthroplasty population. As was already established, MTX has been shown to be effective in treating OA prior to arthroplasty. Given that MTX is not harmful in the perioperative setting, it remains to be seen if there is utility in using MTX to treat post-operative pain in post-operative osteoarthritic joint replacements. This review's purpose is to review the available literature surrounding the functional impacts of MTX on arthroplasty outcomes and lay the groundwork for additional research on the impacts of MTX on functional outcomes in osteoarthritic joint replacements.

Materials and Methods

Publications were queried using PUBMED and OVID MEDLINE for a list of keyword and MESH heading searches. We used the following terms: arthroplasty, joint replacement, methotrexate, DMARDs, osteoarthritis, rheumatoid arthritis, arthritis, and combinations of these keywords. After removal of duplicates, over 159 results resulted from this initial search strategy. Abstract and title analysis was used to narrow the application of exclusion criteria, any remaining publications were subjected to detailed review. After application of the exclusion criteria as detailed in Figure 1, 12 different publications remained. Search results were generated and reviewed by a second independent reviewer.

Exclusion criteria included infection as an only outcome, case reports, review articles, non-English literature, histopathological or biochemical outcomes only, and follow-up less than 3 months.

Results

The pertinent findings of each paper included in this systematic review are summarized in Table 1. In total, we included 11 retrospective studies and 1 case control study. The number of participants in these papers ranged from 20 patients to 125,525 patients. Follow up times ranged from 6 months to over 18 years, and outcome measures ranged from functional outcomes like ROM to surgical outcomes like the number of revisions. Taken together, the evidence discussed in this review would suggest that MTX use does not lead to worse patient outcomes.

We used the GRADE system to rank the quality of evidence of each of the studies included in this review.[21] These studies are all retrospective in nature, making them inherently "Low" evidence under the GRADE framework. Regarding the outcome of methotrexate, the risk of bias in these studies was high, causing us to further downgrade the evidence quality to "very low" for all studies included in this review. We believe that the poor quality of research available to date reflects the novelty of the clinical question being posed in this review.

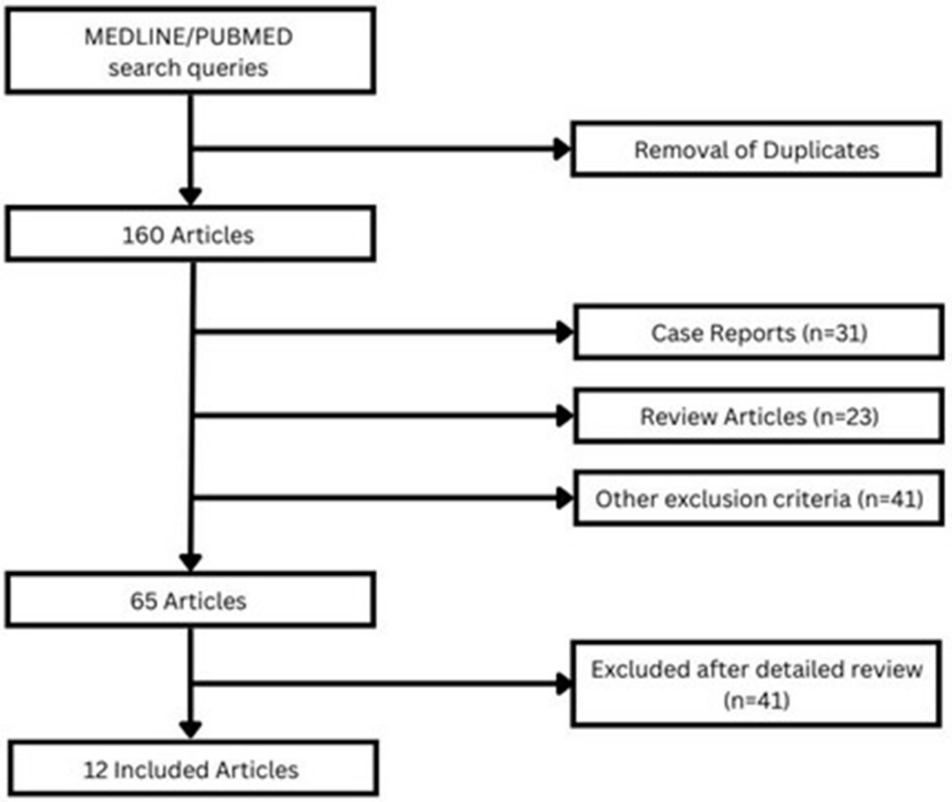

Figure 1 Flowchart of included articles.

Discussion

To date, the evidence surrounding MTX use in arthritis applies mostly to the immediate perioperative period and risk of surgical site infection. This study represents a review of the body of evidence pertaining to clinical outcomes associated with MTX usage. In this review, only one publication reports detriment with regards to nerve function while all other studies reveal no difference in revision rate or postoperative pain and function scores. Here we demonstrate that further

Table 1 Detailed Descriptions of the Included Studies

Article	Joint	Patient No.	Study Type	Endpoints	Results	Mean Follow-up	Conclusion
Yamashita et al 2020[10]	TKA	142 (82 on MTX)	Retrospective	Japanese orthopedic score, ROM, revisions, ability to ambulate indoors	96.6% survival all TKA at 10.6 years	10.6 years	MTX not associated with increased walking difficulty
Mangold et al 2019[11]	RSA	91 (19 on MTX)	Retrospective	Revision rate, arthroplasty survival, ASES, SST, ROM	2 and 5 year re-operation free rate was 97%	4 years	No variables analysed in this study had an impact on revision surgery
Hernigou et al 2017[12]	TKA	45 RA, 45 OA, all of which are revision	Retrospective	KSS, revision rate, loosening/lines	Re-revision rate 9% in RA, 15% OA patients.	10 years	No significant increase in revision rate or radiolucent lines associated with MTX.
Nishikawa et al 2014[13]	TKA	30 RA patients	Retrospective	ROM, MHAQ, CRP, KSS, DAS	KSS avg 91. Avg function score 51/poor	142 months	Disease activity decreased at 10 years with MTX usage.
Kanbe et al 2015[14]	Any	20 Arthroplasty patients with non-responding RA	Retrospective	RA remission	DAS, CRP, improved in patient using MTX/combo	1.15 years	Arthroplasty effective at obtaining disease remission with MTX/Biologic

(*Continued*)

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Table 1 (Continued).

Article	Joint	Patient No.	Study Type	Endpoints	Results	Mean Follow-up	Conclusion
Malviya et al 2011[15]	THA	47 JIA pts with THA, 11 using MTX	Retrospective	WOMAC, survival of THA	THA survival significantly improved with MTX use	18.7 years	Not using MTX reduces survival time of THA
Hurowitz et al 2007[16]	TAR	65 TAR, 10 RA patients 3 using MTX	Retrospective	Revision, amputation	At 6 years total 67% survivorship of TAR	3.3 years	Smoking, DM, MTX not associated with adverse TAR outcome.
Lynch et al 1996[17]	TSA	378 patients, 5 using MTX	Retrospective	Neurological injury and function, resolution, graded on seddon or sunderland	18 neurological injuries 3/5 mtx patients included.	2 years	Possible attribution of postop neuro injury with MTX use in TSA
Perhala et al 1991[18]	THA or TKA	60 RA patients with 92 arthroplasties, 110 TJA RA controls	Case Control	Clinical signs of superficial or deep infection, bloodwork	8.7% complications in MTX group 5.5% in non-MTX	6 months	Only 1 infection beyond 12 weeks postop
Ren et al 2021[9]	TKA	56 pts with 91 TKAs, 25 patients using MTX	Retrospective	HSS score, complications, labwork	DMARDs did not improve VAS or HSS score, No revisions required	11.4 years	DMARDs did not demonstrate pain improvement, may have addition effect with GCs
Cordtz et al[19]	THA or TKA	3913 RA patients, 120,499 OA patients in Denmark	Retrospective	Revision, prosthetic infection	10 risk of revision (0.52–2.41) and 1 year PJI (0.79 to 3.06)	5.47 years	No increase in revision or PJI rates at 1 and 10 years relative to OA.
Jeyaraman, M[20]	TKA	47 TKA patients with RA in India	Retrospective	KSS	69% of patients were on MTX, Postop scores were improved (p=0.004)	37 months	MTX had a significant associated increase in KSS relative to pre-op

Abbreviations: ASES, American shoulder and elbow surgeons score; CRP, c reactive protein; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; GC, glucocorticoid; HSS, hip society score; JIA, juvenile idiopathic arthritis; KSS, knee society score; MHAQ, modified health assessment questionnaire; MTX, methotrexate; OA, osteoarthritis; PJI prosthetic joint infection; RA, rheumatoid arthritis; ROM, range of motion; RSA, reverse shoulder arthroplasty; SST, simple shoulder test; TAR, total ankle replacement; THA, total hip arthroplasty; TJA, total joint arthroplasty; TKA, total knee arthroplasty; TSA, total shoulder arthroplasty; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

research and focus is needed with the potential to perform pilot studies examining the use of MTX as an adjunct for post arthroplasty pain and functional benefit.

Our search included all large joint arthroplasty in order to broaden our search from focusing on a specific large joint. A large body of research generated by our search criteria addressed the concerns around immediate perioperative wound complications of MTX. This question itself has mostly resulted in recommendations for continuation of the drug through the perioperative period.[3,11]

Only 6 studies presented in Table 1 collected post operative functional data or scoring assessments such as range of motion (ROM), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Hip Society Score (HSS) and the Knee Society Score (KSS). The remainder of the studies focused on long-term incidence of infection and the need for revision surgeries. This highlights a relative paucity of clinically useful research regarding MTX in arthroplasty patients and emphasizes the need for further investigations to explore the impact of MTX on functional outcomes.

An interesting population that surfaced in this search involved juvenile idiopathic arthritis (JIA) patients undergoing arthroplasty. These patients appeared to benefit from methotrexate usage both before and after total joint replacements.[15] JIA patients using MTX experienced both prolonged time to arthroplasty and prolonged arthroplasty longevity. Given that JIA patients are much younger than the average arthroplasty patient, the JIA patient population represents an ideal model for the study of MTX effect on long term outcomes.

Another unique aspect from our point of view is the increase in percentage of patients on MTX at the end of the study done Nishikawa et al.[10] While this could indicate that the patient population is experiencing worsening RA, it also could mean that the symptoms of pain and function that were tolerable in post-op total knee arthroplasty (TKA) patients could be maintained by these increased doses of MTX.

One study investigating the use of perioperative MTX in total shoulder arthroplasty reported a postoperative increase in neurological complications.[17] This study may have been underpowered with only 5 instances of patients with methotrexate seen in that population and 1 patient included twice for separate complications.

Only the study by Jeyaraman et al demonstrated a specific analysis of the effects of MTX on postoperative function scores.[20] This represents the most powerful evidence in our collection that MTX may have a specifically beneficial effect for arthroplasty patients.

To our knowledge this review provides the only collection of papers that have been put together regarding the clinical question of whether methotrexate has any effect on metrics such as functional outcomes when used in patients post-arthroplasty. Included here are studies of ankle, shoulder, knee and hip arthroplasties, allowing a starting point for future methotrexate-based research into post-arthroplasty outcomes in each of these settings. This review demonstrates that this question is novel in nature and any specific research put forth towards answering this question is likely to have a large impact on the quality of evidence in this regard.

Significant limitations noted throughout the presented literature involved the vast majority of patients being female, MTX's effect typically being a subgroup analysis, and poorly powered studies. Additionally, the evidence presented in this review is considered "very low" according to the GRADE system. These limitations may undermine the extraction of clinical conclusions regarding MTX but further emphasize the need for additional primary literature into the topic.

Conclusion

In summary, our search of available evidence presented here represents a better picture of MTX and its effect on arthroplasty outside of the immediate perioperative period. With much of the available body being recent literature, it seems to indicate that there is a role for further research into the specific outcomes of MTX and its clinical effects post arthroplasty. The available research is of very low quality, and heterogenous in population and outcome measures. However, throughout this wide sampling of patients, MTX does not appear to have detrimental effect on arthroplasty outcomes with no significant increase in revisions or long-term infections reported. This review should suffice as a building block for further investigations and trials into MTX's utility for arthroplasty patients. Our goal in publishing this paper would be to increase the prevalence of MTX use as a sub-analysis of arthroplasty papers with clinical and patient-reported outcome measures.

Disclosure

The authors report no conflicts of interest in this work.

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