REVIEW

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Pharmacological prevention of arthrofibrosis: a systematic review

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Background and aims: Arthrofibrosis is a complication of intra-articular knee surgery which is caused by intra-articular fibrosis. To date, several preventive therapies for arthrofibrosis have been reported. This systematic review aims to summarize current knowledge about pharmacological arthrofibrosis prevention. Methods: A systematic literature search was conducted in Medline, Web of Science, and Cochrane library using the search term 'Arthrofibrosis AND prevention'. Subsequently, articles reporting the effects of a preventive pharmacological intervention against arthrofibrosis were included in this review. Results: 16 studies investigated the pharmacological prevention of arthrofibrosis of which 13 were conducted in animal models. Several drugs improved the range of motion (ROM) in animal models. Bevacizumab (ROM +39.4 degrees), nonsteroidal anti-inflammatory drugs (ROM +18.0-31.2 degrees), and rosiglitazone (ROM +19.5 degrees) significantly increased the ROM. Artesunate, mitomycin c, bevacizumab, hyaloglide, and botulinum toxin A significantly reduced adhesion scores. None of the drugs tested in humans improved the functional outcomes after joint arthroplasty. Methodological differences limited the ability to compare outcomes and, due to poor reporting of methodology, many studies had an unclear risk of bias. Conclusion: This review identified several drugs as potential candidates for arthrofibrosis prevention. These drugs modulate inflammation or alter the activity of fibroblasts. Most studies are conducted in experimental animal models and none of these results are currently translated into a clinical application. Moreover, the methodology and route of administration varied between studies. Nor were dose dependency studies conducted. Future studies should adopt a standardized approach to determine the effects of preventive pharmacological interventions on arthrofibrosis.

Keywords: Arthrofibrosis, postoperative joint stiffness, intra-articular fibrosis, adhesions.

Abbreviations:

DMSO	Dimethyl sulfoxide;
FC	Flexion contracture I
A	Intra-articular route of administration
PBS	Phosphate buffered saline
ROM	Range Of Motion
TGFβ	Transforming Growth Factor Beta
TKA	Total knee arthroplasty
TNFα	Tumor Necrosis Factor Alpha
VEGF	Vascular Endothelial Growth Factor

INTRODUCTION

Arthrofibrosis is a common and invalidating complication of intra-articular knee surgery, most often observed after reconstructive ligament surgery or total knee arthroplasty. Arthrofibrosis is characterized by the formation of intra-articular fibrotic tissue, which causes a reduced range of motion (ROM) and stiffness of the knee, thus dramatically compromising the postoperative function. Knee arthrofibrosis is usually accompanied by pain, loss of strength and the inability to perform normal postoperative levels of physical activity[1].

Arthrofibrosis is the result of a complex interaction between surgery-induced tissue damage, the release of inflammatory mediators by inflammatory cells, and the stimulation of fibroblasts into the production of extracellular matrix[2]. To date, the exact pathophysiology of arthrofibrosis has not been fully elucidated. Current evidence suggests that after an injury or after surgery,

damage to the intra-articular tissues causes hypoxia and the activation of the inflammasome. This causes the recruitment and activation of macrophages, mast cells and T-lymphocytes, which release a large number of inflammatory mediators such as interleukin 1, interleukin 6, tumor necrosis factor α (TNFα), platelet-derived growth factor and transforming growth factor beta (TGFβ). This proinflammatory immune activation promotes the recruitment of fibroblasts to the injury site and causes an imbalance between extracellular matrix deposition and degradation. As a result, a dense network of mostly collagen I fibers is constructed with extensive cross-linking between the fibers[2]. This cross-linking prevents efficient apoptosis, autophagy, and matrix degradation by matrix metalloproteinases after the injury-induced inflammation starts to diminish.

Once arthrofibrosis is present, early treatment is advised[3]. Sometimes physiotherapy, anti-inflammatory drugs, corticosteroids or manipulation under anesthesia can already sufficiently decrease the stiffness of the knee[3]. If this is insufficient, arthroscopic or open surgical interventions are often necessary, often with moderate functional outcomes[4]. For this reason, preventing arthrofibrosis from developing and maturing is crucial. Many studies have demonstrated that immediate postoperative mobilization and physiotherapy are efficacious in reducing arthrofibrosis[2,5]. Yet, they are unable to completely prevent it. For this reason, several studies attempted to pharmacologically prevent arthrofibrosis from occurring.

This systematic review aims to summarize current clinical and experimental literature on the pharmacological prevention of arthrofibrosis and how such treatments could be clinically applied in patients undergoing reconstructive knee surgery.

MATERIALS AND METHODS

Search strategy

Between August 2021 and October 2021 a systematic literature search and review was conducted in the databases of Medline, Web of Science and Cochrane Library. To maximize the retrieval of articles that describe the pharmacological prevention of arthrofibrosis, an inclusive search term without any additional filters was used: 'Arthrofibrosis AND prevention'.

Study Selection

Articles retrieved using the aforementioned search strategy were independently reviewed using a two-stage selection method by two reviewers (ER and PP). During the first stage, duplicates were removed and articles were screened based on their title and abstract. Only experimental, prospective or retrospective studies were included at this point. Any type of review, including meta-analyses and systematic reviews, were excluded. Since this systematic review aimed to investigate clinical but also experimental methods in preventing arthrofibrosis, both human and animal studies were included. Furthermore, studies that were not available in English, without a control group, or did not have any type of pharmacological intervention were also excluded in the first stage. When the abstract did not contain sufficient information to decide about inclusion or exclusion, it was carried over to the second selection stage. In this second stage, the remaining studies were assessed based on the contents of their full text. Articles were included if they specifically aimed to prevent arthrofibrosis by pharmacological therapy, if they included a control group and if random group allocation was present. If a study compared pharmacological interventions for arthrofibrosis and both of the reviewers agreed on the inclusion, it was included in the systematic review.

Data extraction

A large heterogeneity between the different studies was already observed during the inclusion process. Therefore a large number of variables and study characteristics were extracted from the different studies. Data extraction included: Type of study, year of publication, the aim of the study, sample size, duration of follow-up, pharmacological properties (type of drug, dose, timing of administration, frequency of administration, method of administration, vehicle), the trigger/method by which arthrofibrosis was induced, the outcomes and how these outcomes were measured.

Data reporting and statistical analysis

Functional outcomes were reported as the range of motion (ROM) or the flexion contracture; the latter defined as the inability to fully extend the joint, both expressed by the number of degrees. Adhesion scores were based on the modified Rothkopf adhesion score (0, no adhesions; 1, filmy, weak fibrous tissues removable by minimal traction/gravity; 2, moderate fibrous tissues separable by manual traction; 3, firm and dense fibrous tissues only surgically removable).

Statistical analysis was performed using Review Manager (Version 5.3, The Cochrane Collaboration,

Copenhagen) and R 4.1.1 (R Core Team, 2021; forestplot package v2.0.1)[6]. Adjusted means with 95% confidence intervals (95% CI) were calculated using a random-effects model. Outcomes of the different studies were graphically displayed as forest plots and categorized based on the type of therapy and weeks after the induction of arthrofibrosis. Due to differences in methodology and treatments, the results of different studies were not pooled except to calculate the differences in ROM/flexion contracture for the control groups.

Quality of the included studies was assessed using SYRCLE's risk of bias tool for animal studies and Cochrane's risk of bias tool for studies in human subjects[7,8]. Risk of bias was classified as low risk, high risk or unclear risk.

RESULTS

Study selection and overview

Using the search term described above, 187 studies were retrieved (Figure 1). Following the removal of duplicates (n=32) and after screening on title and abstract, 27 studies remained. Additionally, 11 studies were excluded based on the analysis of the full text, mainly because the articles did not have arthrofibrosis as a primary aim or because only *in-vitro* data was reported. As a result, a total of 16 studies were included

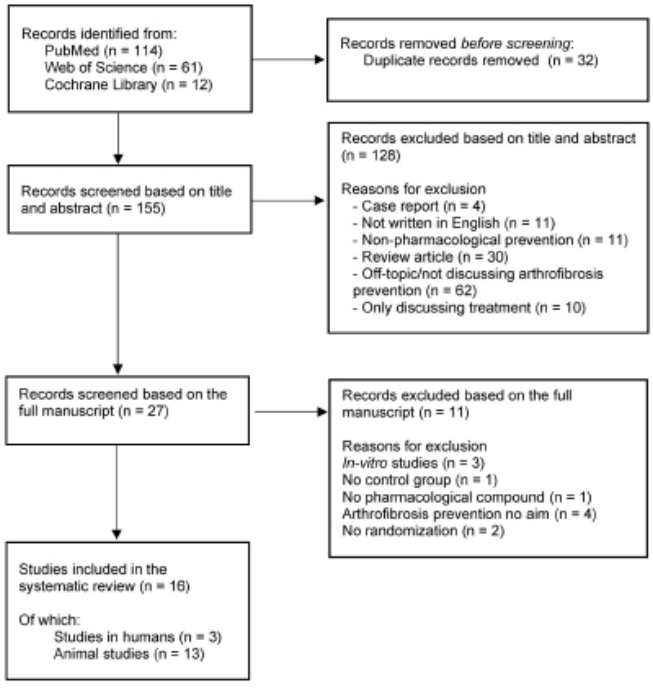

Figure 1. – Study inclusion flowchart. Overview of the inclusion process from initial search to the final study selection.

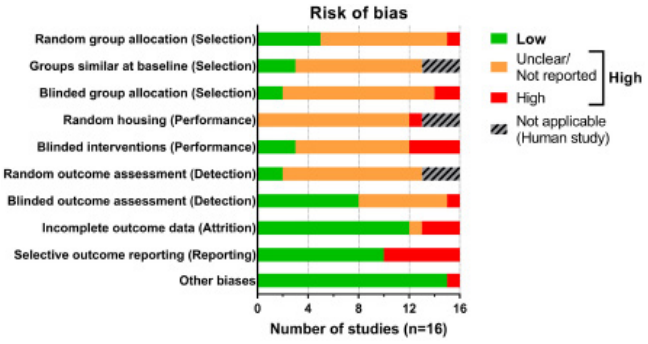

Figure 2. – Risk of bias overview. Risk of bias was assessed using SYRCLE's risk of bias instrument or Cochrane risk-of-bias tool version 2.

in this systematic review[9-24]. Quality and risk of bias are reported in Table I and Figure 2.

The majority of studies (n=13) investigated the preventive effect of a pharmacological intervention on arthrofibrosis in an animal model, with only 3 studies reporting clinical outcomes in human subjects. The included studies were subject to significant differences in methodology and a large number of drugs were tested, often in different dosages or in multitherapy (Table II). Furthermore, a large number of techniques to create arthrofibrosis with variable duration of follow-up have been applied throughout the different studies (Table II and supplementary material). In short, animal models for arthrofibrosis typically induced a joint contracture by creating a bony, ligamentous or capsular defect followed by prolonged immobilization of the limb in a flexed position. Studies in humans all reported outcomes following total knee arthroplasty. To determine the effects of the pharmacological intervention, various outcome measures were used. In general, the effects of pharmacological prevention of arthrofibrosis were reported as the effect on functional outcomes, the macroscopic visualization of intra-articular adhesions, and differences in histology.

Effects on joint mobility

Following surgery and immobilization, vehicle-treated animals had an average adjusted ROM of 52.8 degrees (95% CI 47.7-57.9) after 7-8 weeks, which increased to an average ROM of 66.5 degrees (95% CI 56.2-76.9) after 16-24 weeks. The flexion contracture meanwhile decreased by 22.9 degrees (95% CI 7.1-38.7) within 16-24 weeks.

Three studies tested the effects of a nonsteroidal anti-inflammatory drug for preventing arthrofibrosis (Figure 3)[18,20,22]. Compared to vehicle-treated rabbits, intra-articular (IA) administration of celecoxib 200-

Table I. – Overview of the risk of bias assessment

	Year	Animal/human subjects	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
Arsoy et al. (9)	2018	Animal	?*	?	?	+	+	+
Behrend et al. (10)	2019	Human	+	+	+	?	+	+
Brunelli et al. (11)	2005	Animal	?*	?*	+	+	-	+
Efird et al. (12)	2014	Animal	?*	-	?	+	+	+
Emami et al. (13)	2012	Animal	?	?	?	+	-	+
Emami et al. (14)	2012	Animal	?	?	?*	+	+	+
Everts et al. (15)	2012	Human	-	?	?	-	-	-
Gao et al. (16)	2017	Animal	?	?	?*	+	+	+
Kim et al. (17)	2019	Human	?*	+	+	+	+	+
Limberg et al. (18)	2020	Animal	?	?	?	+	+	+
Namazi et al. (19)	2007	Animal	?*	-	?*	+	-	+
Salib et al. (20)	2019	Animal	?	-	-	-	-	+
Steplewski et al. (21)	2017	Animal	-	-	?	+	+	+
Tang et al. (22)	2018	Animal	?	?	?*	-	-	+
Wan et al. (23)	2019	Animal	?	?	?	+	+	+
Yan et al. (24)	2010	Animal	?	-	+	+	+	+

Overview of the quality appraisal of the included studies. Experiments conducted in animal models were assessed using SYRCLE's risk of bias instrument[7]. The quality of randomized controlled trials in humans was assessed using Cochrane risk-of-bias tool version 2[8]. + indicates low risk of bias, ? indicates unclear risk of bias, - indicates high risk of bias. For each type of bias the lowest score is displayed. An asterisk (*) indicates that some of the questions in the bias category were scored as low risk of bias. For a detailed overview of the risk of bias appraisal we refer to supplementary material 1.

400 mg/day increased the ROM by 19.7 degrees (95% CI 5.0-34.4, p=0.009) after 8 weeks and up to 26.0 degrees (95% CI 8.6-43.4, p=0.003) after 24 weeks[20]. When celecoxib was coated onto a membrane the ROM further increased by 31.2 degrees (95% CI 16.4-46.0, p<0.001) compared to the vehicle group[18]. Diclofenac IA 0.5 mg improved the ROM by 18 degrees (95% CI 6.5-29.5, p=0.002) after 8 weeks[22].

The effects of corticosteroids on joint mobility were only investigated by two studies. Triamcinolone IA 0.68 mg/kg reduced the flexion contracture by 25.0 degrees (95% CI 19.2-30.8, p<0.001) two weeks following surgery (Figure 3). Preventive treatment with dexamethasone IA decreased the flexion contracture by 12.1 degrees (95% CI 0.1-24.1, p=0.048) 8 weeks after open joint surgery.

Treatment with biologicals such as bevacizumab (anti-VEGF, IA) and pegylated anti-alpha2Ct antibody (COL1A antibody, IA) also managed to increase the ROM by 39.4 degrees (95% CI 26.5-52.3, p<0.001) and 11.4 degrees (95% CI 0.2-22.6, p=0.046) respectively[13,21]. For a complete overview of the preventive effects of the different drugs on the ROM/flexion contracture we refer to Figure 3.

In humans, vitamin C (oral), platelet gel with fibrin sealant (IA), and a temperature-sensitive anti-adhesive poloxamer (IA) were tested[10,15,17]. None of these drugs affected the long-term ROM after total knee arthroplasty, although the fibrin sealant was able to significantly reduce the incidence of arthrofibrosis.

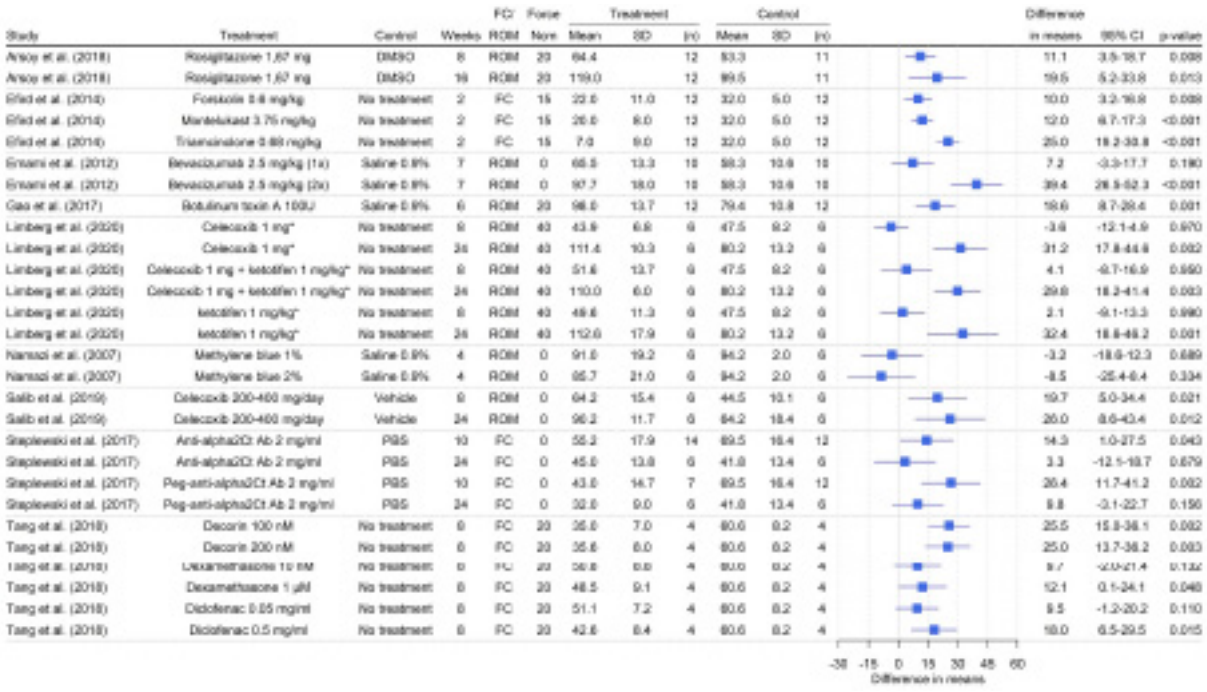

Figure 3. – Effects on range of motion (ROM)/flexion contracture (FC). Forest plots indicate the difference in means and 95% confidence interval (95% CI) between the investigated drug and the control group. An asterisk indicates that celecoxib was coated on a resorbable membrane or that a membrane was used as a vehicle. FC, flexion contracture; PBS, phosphate buffered saline; SD, standard deviation; ROM, range of motion.

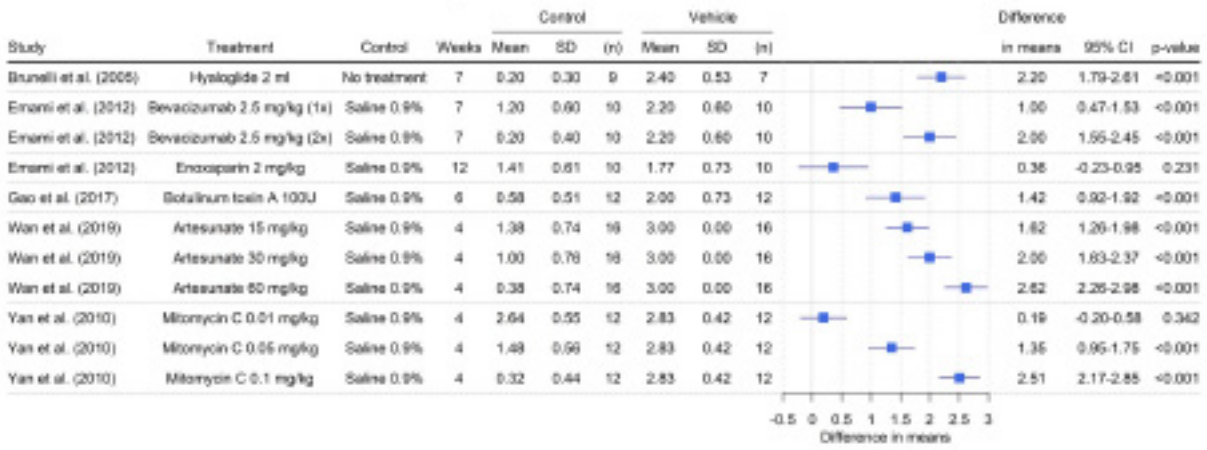

Figure 4. – Differences in adhesion scores. Forest plots show the difference in means and 95% confidence interval (95% CI) between the investigated drug and the control group for the reported adhesion scores. Higher differences in means indicates a bigger difference, thus lower adhesion scores, between het vehicle and drug-treated group. SD, standard deviation.

Macroscopic adhesion formation

Vehicle-treated animals had an average modified Rothkopf adhesion score of 2.40 (95% CI 1.99-2.81). Adhesion scores tended to decrease if the time after the surgical induction of arthrofibrosis increased (p=0.053). A cross-study analysis revealed that differences between animal models resulted in no significant difference in adhesion scores of vehicle-treated animals.

The highest reduction in adhesion scores was seen following treatment with mitomycin C (Chemotherapeutic agent, IA 0.1 mg/kg) and artesunate (antimalarial drug, intragastric 60 mg/kg), showing an absolute mean reduction of 88.7% and 87.3% respectively (Figure 4)[23,24]. In contrast, mitomycin C dosed at 0.01 mg/kg failed to significantly reduce adhesion scores (Figure 4)[24].

Microscopic effects

In animal studies, a dose-dependent effect of bevacizumab was observed, significantly lowering the number of fibroblasts, collagen deposition, vascular proliferation, and amount of inflammatory cells[13]. Furthermore, decreased fibroblast counts were observed on histology following preventive treatment with botulinum toxin A, artesunate, and mitomycin C[16,23,24].

DISCUSSION

Arthrofibrosis has an estimated incidence of around 5% after knee arthroplasty and anterior cruciate ligament repair, but varies between 1-13% in literature[25,2]. It is therefore frequently encountered in knee surgery. While therapy can frequently improve the function successful, prevention of arthrofibrosis is usually advocated as the best treatment[4]. In recent years, the popularity of arthrofibrosis research has soared, resulting in a threefold increase in the number of published studies in 10 years. This has also led to a growing interest in the pharmacological prevention of arthrofibrosis. This systematic review summarizes the current literature on pharmacological prevention and/or modulation of arthrofibrosis.

To date, several studies demonstrated a reduced incidence of arthrofibrosis using existing and experimental molecules in a preventive setup. These experimental studies, mostly conducted in animal models, used a large variety of molecules with different mechanisms of action to inhibit the development of arthrofibrosis indicating the involvement of several pathways.

One of the principal requirements for arthrofibrosis is inflammation which upregulates TGFβ and promotes excessive extracellular matrix synthesis by fibroblasts[2]. Our results indicate that preventive strategies that modulate this inflammatory response were superior. In their study, Limberg et al. were able to increase the ROM by over 30% following the intra-articular implantation of a celecoxib-coated membrane in a rabbit model for arthrofibrosis[18]. Likewise, intra-articular administrations of celecoxib or diclofenac also showed high efficacy in reducing arthrofibrosis[20,22]. Reduced arthrofibrosis, although less substantial and hardly dose-dependent, was also observed after administering corticosteroids[12,22].

A second group of drugs that exerted a significant preventive effect on arthrofibrosis were the anti-proliferative drugs such as bevacizumab and mitomycin C[13,24]. Both drugs increased the ROM after open knee surgery and reduced the macroscopic formation of fibrous adhesions. This is presumably related to the immediate reduction of fibroblastic activity and limiting the maturation of adhesions. Their role in preventing adhesions has already more substantially been reported in peritoneal adhesiogenesis[27-29].

Another approach to pharmacologically reduce arthro-fibrosis was the direct interference with the collagen formation by blocking the collagen-collagen interaction of collagen I molecules using intra-articular administered recombinant anti-alpha2Ct antibody[21]. Ten weeks after surgery, including 8 weeks of immobilization, a 20% reduction in flexion contracture was seen compared to the vehicle-treated group. By using a pegylated anti-alpha2Ct antibody the effect even increased up to 40%. However, 24 weeks after surgery the effect of anti-alpha2Ct antibodies diminished and its impact on the flexion contracture became indistinguishable from the vehicle-treated group[21].

For other drugs, the mechanism of action is less clear. Artesunate, an antimalarial drug, strongly reduced adhesion scores[23]. It is presumed that artesunate acts on arthrofibrosis by suppressing fibroblast proliferation although the precise mechanism is not fully established[30]. Similarly, several studies have reported an anti-fibrogenic effect of rosiglitazone, an anti-diabetic drug that acts as a PPAR-γ agonist[31,32]. Indeed a 17.8% increase in ROM was observed 16 weeks after knee joint surgery[9].

Although this systematic review offers numerous leads for future research, it also shows the lack of standardized, long-term, and translational research. Studies demonstrated important methodological differences and often the methodology was not fully described, resulting in an unclear risk of bias. Although most surgical interventions to create an intra-articular defect were mechanistically similar in most studies, substantial differences remain. Moreover, not a single compound except for Celecoxib was investigated in more than one study. Furthermore, the way arthrofibrosis was defined and diagnosed also differed between studies. The majority of studies reported preventive effects on functional outcomes such as range of motion or joint flexion/extension contracture often against a certain amount of force. However, additional outcomes such as a modified adhesion score, histological investigations and molecular techniques were also often used as indicators for an effect of a drug on arthrofibrosis. This lack of standardization strongly limited the analysis and comparison of

results. Therefore this systematic review is unable to draw strong conclusions on which pharmacological intervention is superior in preventing arthrofibrosis.

Another limitation of the currently available literature is the lack of translational research. Almost none of the presented drugs have been translated into a clinical study. Therefore, it is currently impossible to predict how these compounds would improve clinical outcomes. Similarly, it is unknown how these drugs would result in side effects by affecting wound healing, prosthesis ingrowth or capsular stability.

To further advance in the field of arthrofibrosis prevention we believe that standardizing the methodology of arthrofibrosis research is a priority. Reported outcomes should include the ROM, adhesion severity and occurrence of complications. Moreover, future studies should focus on compounds that directly act on the involved inflammatory or fibrosis pathways, as these compounds proved to be the most effective in our systematic review. Ideally, such a drug is administered directly intra-articular during the procedure and administered in a long-acting gel or resorbable membrane. Finally, after extensive testing in animal models with varying extent of articular damage and varying immobilization a translation to humans should be made.

In conclusion, this systematic review investigated current evidence for the pharmacological prevention of arthrofibrosis. While numerous compounds have been investigated, drugs that acted on the inflammatory pathways or modulated fibroblast proliferation were most efficacious in preventing arthrofibrosis. However, not a single experiment was repeated in an independent study nor translated into a clinical study. Current literature is characterized by considerable differences in experimental models, compounds and techniques to assess the outcomes. Future studies should prioritize a standardized methodological approach.

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