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Intra-articular celecoxib improves knee extension regardless of surgical release in a rabbit model of arthrofibrosis

W. H. Trousdale,
A. K. Limberg,
N. Reina,
C. G. Salib,
R. Thaler,
A. Dudakovic,
D. J. Berry,
M. E. Morrey,
J. Sanchez-Sotelo,
A. van Wijnen,
M. P. Abdel

From Mayo Clinic, Rochester, Minnesota, USA

Aims

Outcomes of current operative treatments for arthrofibrosis after total knee arthroplasty (TKA) are not consistently positive or predictable. Pharmacological in vivo studies have focused mostly on prevention of arthrofibrosis. This study used a rabbit model to evaluate intra-articular (IA) effects of celecoxib in treating contracted knees alone, or in combination with capsular release.

Methods

A total of 24 rabbits underwent contracture-forming surgery with knee immobilization followed by remobilization surgery at eight weeks. At remobilization, one cohort underwent capsular release (n = 12), while the other cohort did not (n = 12). Both groups were divided into two subcohorts (n = 6 each) – one receiving IA injections of celecoxib, and the other receiving injections of vehicle solution (injections every day for two weeks after remobilization). Passive extension angle (PEA) was assessed in live rabbits at 10, 16, and 24 weeks, and disarticulated limbs were analyzed for capsular stiffness at 24 weeks.

Results

IA celecoxib resulted in greater mean PEA at ten weeks (69.6° (SD 4.6) vs 45.2° (SD 9.6), p = 0.004), 16 weeks (109.8° (SD 24.2) vs 60.9° (SD10.9), p = 0.004), and 24 weeks (101.0° (SD 8.0) vs 66.3° (SD 5.8), p = 0.004). Capsular stiffness was significantly reduced with IA celecoxib (2.72 Newton per cm (N·cm)/° (SD 1.04), p = 0.008), capsular release (2.41 N·cm/° (SD 0.80), p = 0.008), and capsular release combined with IA celecoxib (3.56 N·cm/° (SD 0.99), p = 0.018) relative to IA vehicle (6.09 N·cm/° (SD 1.64)).

Conclusion

IA injections of a celecoxib led to significant improvements in passive extension angles, with reduced capsular stiffness, when administered to rabbit knees with established experimental contracture. Celecoxib was superior to surgical release, and the combination of celecoxib and a surgical release did not provide any additional value.

Article focus

- In a rabbit model of arthrofibrosis, does intra-articular (IA) celecoxib improve motion compared to control injections?
- Is IA celecoxib superior to a capsular release?
- Does IA celecoxib have synergistic effects when combined with a capsular release?

Key messages

- IA celecoxib significantly improves passive range of motion and capsular stiffness in a validated rabbit model of arthrofibrosis.
- IA celecoxib is superior to a capsular release.
- IA celecoxib combined with capsular release did not provide additional value when compared to each treatment alone.

Correspondence should be sent to Matthew P. Abdel; email: abdel.matthew@mayo.edu

Strengths and limitations

- Use of a validated large animal model with relatively high numbers of subjects compared to other, similar studies.

- Direct local administration of the studied drug, thus reducing confounding variables compared to studies using subcutaneous or oral drug delivery.

- A limitation of this study is a lack of molecular and histological data to confirm tissue-specific changes.

Introduction

Arthrofibrosis is a debilitating complication affecting roughly 4% of all patients undergoing primary total knee arthroplasty (TKA).[1,2] Arthrofibrosis also complicates various other orthopaedic procedures and injuries. Nonoperative treatment options for this disease are limited, and in many cases a surgical capsular release in the form of a lysis of adhesions (LOA) is performed, often combined with exchange of one or more prosthetic components.[3-17] Yet, these patients' knees are often refractory to operative treatment as arthrofibrosis can recur after capsular release.[6,14,18-20] Thus, the persistently stiff knee is a clinical challenge that would benefit from new adjuvant therapies.

Currently, there are limited pharmacological treatments for the established arthrofibrotic knee. Almost all in vivo animal studies focus on the prevention of joint contractures, with only one examining the treatment of established contractures.[21] Moreover, there are no studies comparing pharmacological treatment to a surgical capsular release, and no studies investigating the possible synergistic effect of combining the two.

Previous studies laid the groundwork for evaluating the effectiveness of pharmacological methods in treating established contractures and comparing these treatments to a capsular release.[22-26] Several studies have shown the effectiveness of celecoxib, a selective cyclooxygenase-2 inhibitor, in preventing the formation of scar tissue in our animal model of arthrofibrosis.[24,25,27] Additionally, Barlow et al[28] previously developed a modified rabbit model with a limited surgical release of an established contracture. In that investigation, authors showed a significant improvement in passive extension angles (PEAs) in the surgically treated contractures.[28]

The current study investigated adjuvant therapies for treatment of an established contracture through three aims. The first aim was to investigate the biomechanical effects of intra-articular (IA) celecoxib injections for the treatment of established contractures in a rabbit model of arthrofibrosis. The second aim was to compare IA celecoxib injections to a surgical capsular release. The final and third aim was to investigate the potential additive effects of combining IA celecoxib and capsular release.

Methods

Study design. Animal care committee approval (IACUC) was obtained and the ARRIVE checklist was completed to perform a study on 24 skeletally mature New Zealand White (NZW) female rabbits. Each rabbit underwent a contracture-forming surgery followed by immobilization of the right knee as previously described (Figure 1).[2,22–26,28–33] After eight weeks of immobilization in a 1 m^3 cage, all rabbits underwent a remobilization procedure, which involved general anaesthesia and removal of the Kirschner wire (K-wire). After K-wire removal, 12 of the 24 rabbits underwent a capsular release procedure as previously described.[28] Briefly, this capsular release involved a lateral incision on the right knee with blunt dissection to the lateral meta-diaphysis. An elevator was then inserted posteriorly with periosteal elevation carried to the joint. After K-wire removal and/or capsular release, each group of 12 rabbits (capsular release and non-capsular release) was again divided into two different cohorts – with six rabbits in the capsular release group and six in the non-capsular release group receiving IA celecoxib injections every day for two weeks. The other six rabbits in the capsular release and non-capsular release groups underwent 'sham' injections with the same solution used to dissolve the celecoxib (vehicle solution). By week 10 there were four groups with six rabbits each: capsular release alone, capsular release combined with IA celecoxib injections, celecoxib injections alone, and untreated control with injection of vehicle solution but no capsular release. The injections stopped at week 10 and all rabbits were allowed 14 weeks of free cage activity until sacrifice at 24 weeks.

Preparation of celecoxib and control injections. The methods to prepare the celecoxib drug solution for IA injections has been previously described.[25] 'Sham' injections used a solution identical to the treatment injections, but without the addition of celecoxib. These injections were administered into the joint every day for two weeks (14 days total) after the remobilization surgery at Week 8.

Static joint angle measurement. At the 8-, 10-, 16-, and 24-week timepoints, rabbits were anaesthetized and placed into a validated plunger device.[32] A string tied to the experimental rabbit limb gently extended the knee at three sequential forces (20, 30, and 40 N·cm). A static lateral fluoroscopic image was taken after each force was applied, with the joint angle measured with a digital goniometer (Figure 2).

Dynamic stiffness measurement. At 24 weeks, and following sacrifice, the operative limbs of all animals were disarticulated at the hip and the foot was removed. Skin and other soft-tissues were removed from both the femur and tibia, while taking care to preserve the joint capsule. A 1 cm region of soft-tissue was left on both the femur and tibia nearest to the knee joint. Metal rods were then cemented into the intramedullary canals of the femur and tibia. Once dry, the limb was mounted on a dedicated dynamic load cell device (Figure 3).[29,34] The maximum

Fig. 1
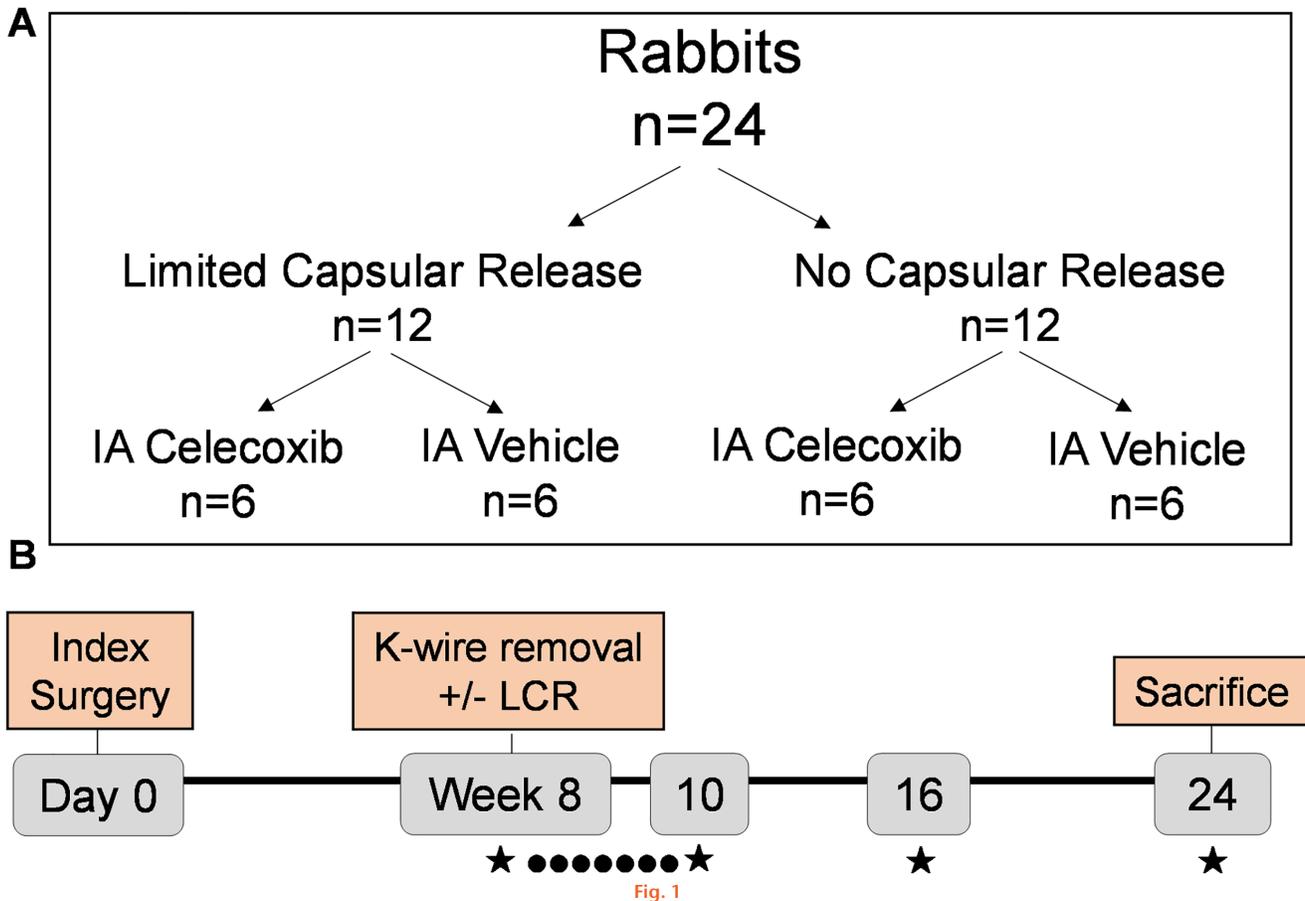
Experimental design: a) 24 rabbits were divided into four groups in order to test effects of limited capsular release (LCR) and intra-articular (IA) celecoxib, both separately and together. b) Over the course of the experiment, contractures were treated every day for two weeks with IA injections of celecoxib or vehicle (●) and assessed (★) at weeks 8, 10, 16, and 24 for passive extension angle. After sacrifice (24 weeks), capsular stiffness was evaluated. K-wire, Kirschner wire.

torque applied to the joint was 20 N·cm and the tibia was moved at a rate of 1°/second. Data were analyzed utilizing Matlab R2019a (Mathworks, USA). A previously defined 'stiffness coefficient' was used to characterize the dynamic stiffness of the joint using the slope of the steepest most linear portion of the exponential curve exported from the load cell device.[26]

Statistical analysis. Data were reported with group means and standard deviations (SDs). Kolmogorov-Smirnov normality tests were performed on all experimental data to determine if parametric (independent-samples t-test) or non-parametric tests (Mann-Whitney U test) should be used for treatment group comparisons. All statistical analyses were carried out using GraphPad Prism Version 9.0.0 for Windows (GraphPad Software, USA). Statistical significance was set at an α level of < 0.05.

Results

Static joint measurements. The experimental baseline for the effects of capsular release in vehicle control rabbits was established by showing that capsular release with vehicle injection significantly increased mean PEA at 16 weeks (91.5° (SD 15.4) vs 60.9° (SD 10.9), respectively, p = 0.015, Mann-Whitney U test) and 24 weeks (84.7°

(SD 11.2) vs 66.3° (SD 5.8), respectively, p = 0.009, Mann-Whitney U test) compared to the vehicle injection group (Table I, Figure 2b to 2c). Notably, IA celecoxib animals showed statistically significant increases in mean PEA compared to the vehicle injection group at ten weeks (69.6° (SD 4.6) vs 45.2° (SD 9.6), respectively, p = 0.004, Mann-Whitney U test), 16 weeks (109.8° (SD 24.2) vs 60.9° (SD 10.9), respectively, p = 0.004, Mann-Whitney U test), and 24 weeks (101.0° (SD 8.0) vs 66.3° (SD 5.8), respectively, p = 0.004, Mann-Whitney U test (Table I, Figure 2a to 2c)). Additionally, the IA celecoxib treatment group showed statistically significant improvement in mean PEAs at 24 weeks compared to the capsular release with vehicle injections (101.0° (SD 8.0) vs 84.7° (SD 11.2), respectively, p = 0.017, Mann-Whitney U test (Figure 2c)). Importantly, no differences were observed when IA celecoxib was combined with a capsular release when compared to the IA vehicle injection with a capsular release (99.2° (SD 17.9) vs 84.7° (SD 11.2), respectively, p = 0.266, Mann-Whitney U test (Figure 2a to 2c)). Similarly, the combination of IA celecoxib and a capsular release had similar PEA when compared with rabbits treated only with IA celecoxib (99.2° (SD 17.9) vs 101° (SD 8.0), respectively, p = 0.738, Mann-Whitney U test
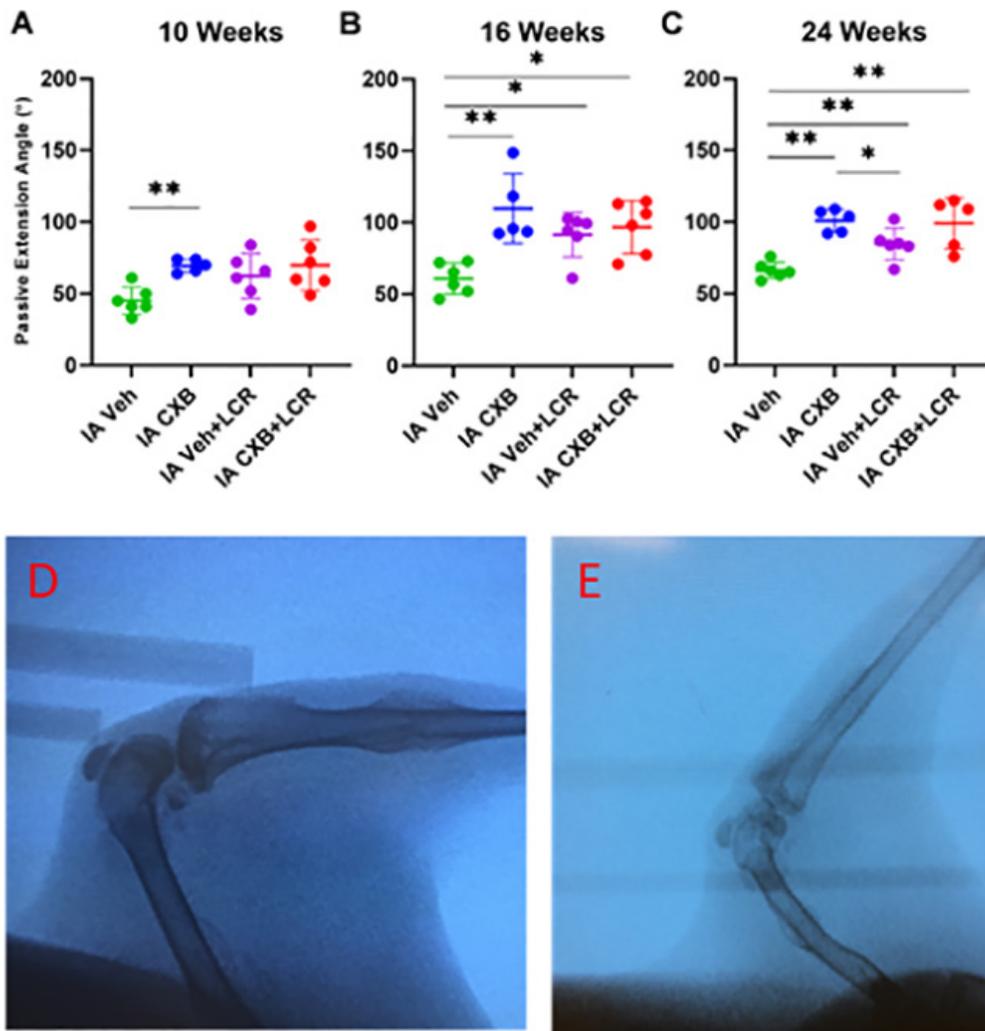
Fig. 2

Intra-articular (IA) celecoxib (CXB) injection increases the passive extension angle (PEA). PEAs were measured fluoroscopically on anaesthetized rabbits (d) and (e) at week 10 (a), week 16 (b), and week 24 (c). The graphs depict mean PEA and standard deviation (n = 5 to 6 for each group), with each data point representing one animal. When applicable, significance is noted with a standard asterisk convention (*p ≤ 0.05, **p ≤ 0.01, Mann-Whitney U test). LCR, limited capsular release. Veh, vehicle.

(Figure 2a to 2c)). Thus, anti-inflammatory intervention using IA celecoxib was found to improve PEA relative to the baseline values with or without surgical release at the experimental endpoint at 24 weeks.

Dynamic stiffness measurement. To corroborate the PEA data, biomechanical load to failure experiments were performed to obtain stiffness coefficients. The mean stiffness coefficient evaluated at 24 weeks was significantly reduced in the capsular release cohort when compared to the vehicle-treated controls (2.41 N·cm/° (SD 0.80) vs 6.09 N·cm/° (SD 1.64); p = 0.008, Mann-Whitney U test (Table II, Figure 3a to 3c)). Similarly, the stiffness coefficient was also significantly reduced in the IA celecoxib group when compared to the vehicle treated controls (2.72 N·cm/° (SD 1.04) vs 6.09 N·cm/° (SD 1.64), respectively; p = 0.008, Mann-Whitney U test). The group with the lowest capsular stiffness was the IA vehicle with capsular release (2.41 N·cm/° (SD 0.80)). The combination

of IA celecoxib with capsular release also significantly reduced capsular stiffness when compared to vehicle-treated group (3.56 N·cm/° (SD 0.99) vs 6.09 N·cm/° (SD 1.64), respectively; p = 0.018, Mann-Whitney U test). Importantly, no statistical differences in stiffness coefficients were observed when comparing IA celecoxib, capsular release, and IA celecoxib combined with capsular release (2.72 N·cm/° (SD 1.04) vs 2.41 N·cm/° (SD 0.80) vs 3.56 N·cm/° (SD 0.99), respectively (Table II)). The stiffness coefficient data largely paralleled the PEA data.

Discussion

Arthrofibrosis after TKA remains a challenging complication, with poor non-surgical and surgical treatment options.[7,26] Arthrofibrosis also complicates other orthopaedic conditions and procedures. For persistently stiff joints, arthroscopic or open lysis of adhesions may be indicated, although with serious limitations, as scar tissue
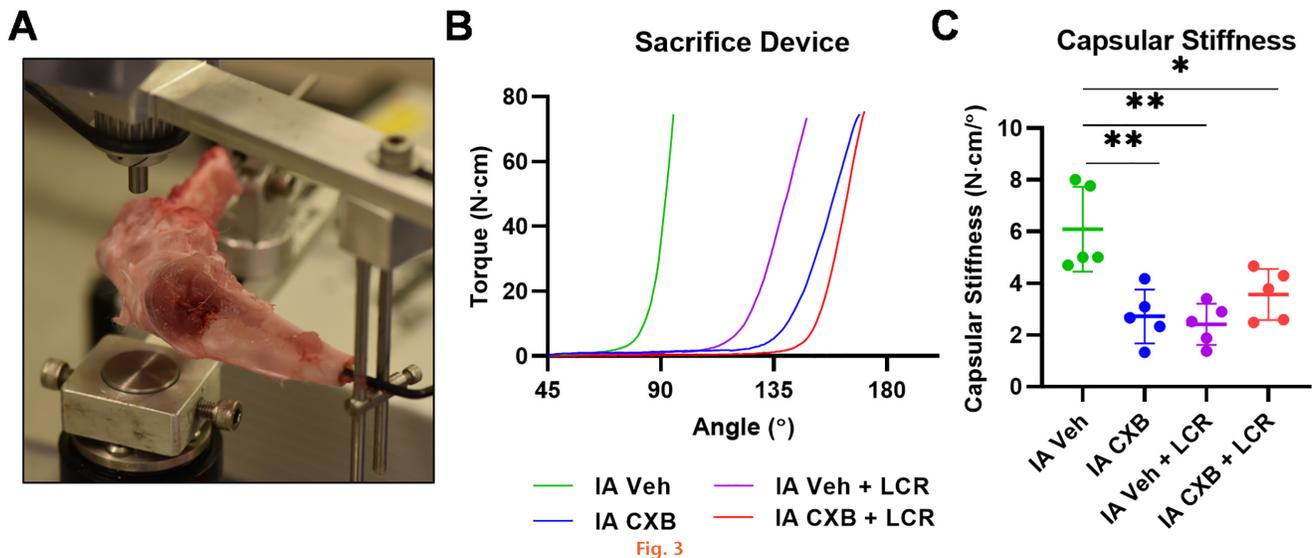
Fig. 3

Intra-articular (IA) celecoxib (CXB) injection reduces capsular stiffness. a) Capsular stiffness measurements were obtained from disarticulated rabbit limbs on a dynamic load cell device after sacrifice at 24 weeks. b) Mean curves generated by the dynamic load cell sacrifice device for each treatment group. c) Capsular stiffness data defined as the slope of a tangential line to the curves shown in panel B. The graphs depict mean capsular stiffness and standard deviation (n = 5 to 6 for each group), with each data point representing one animal. When applicable, significance is noted with a standard asterisk convention (*$p \leq 0.05$, **$p \leq 0.01$, Mann-Whitney U test). LCR, limited capsular release; Veh, vehicle.

Table I. Mean passive extension angles as measured by static pulley device at 40 N·cm for each treatment group. The p-values measure the statistical significance (defined as $p < 0.05$, measured by Mann-Whitney U test) with each treatment group compared to the intra-articular vehicle control group.

Timepoint	IA vehicle, ° (SD)	IA vehicle + LCR, ° (SD)	p-value	IA CXB, ° (SD)	p-value	IA CXB + LCR, ° (SD)	p-value
Week 10	45.2 (9.6)	62.3 (15.7)	0.069	69.6 (4.6)	0.004	69.8 (17.5)	0.023
Week 16	60.9 (10.9)	91.5 (15.4)	0.015	109.8 (24.2)	0.004	96.8 (18.5)	0.009
Week 24	66.3 (5.8)	84.7 (11.2)	0.009	101.0 (8.0)	0.004	99.2 (17.9)	0.007

CXB, celecoxib; IA, intra-articular; LCR, limited capsular release; SD, standard deviation.

Table II. Mean capsular stiffness (N·cm/°) for each treatment group at kill as measured by the dynamic load cell device. The p-values measure the statistical significance (defined as $p < 0.05$, measured by Mann-Whitney U test) with each treatment group compared to the intra-articular vehicle control group.

Group	N·cm/° (SD)	p-value
IA vehicle	6.09 (1.64)	Control
IA vehicle + LCR	2.41 (0.80)	0.008
IA CXB	2.72 (1.04)	0.008
IA CXB + LCR	3.56 (0.99)	0.018

CXB, celecoxib; IA, intra-articular; LCR, limited capsular release; SD, standard deviation.

often reaccumulates, again restricting motion.[35-37] The current study demonstrated that locally administered celecoxib improved range of motion (ROM) in rabbit knees with established contractures. Furthermore, this study showed that local celecoxib treatment was superior to a surgical capsular release alone, and that these two treatment methods combined were not additive or synergistic at improving knee ROM.

The findings in this study are clinically relevant because current treatment options for established contractures are severely limited. Nonoperative treatment options focus on physical therapy and stretching.[9,38] However, these options are often not successful, with physical therapy alone offering just 3° of mean improved motion in one study.[39] For the persistently stiff knee, operative management includes open arthrolysis, arthroscopic lysis of adhesions, and/or a manipulation under anaesthesia (MUA), all with similar levels of improvement.[39] However, 15% of patients are persistently stiff after the MUA.[40,41] For these patients who fail MUA, arthroscopic or open lysis of adhesions has limited success.[42,43] Furthermore, these surgical options are not without risks of periprosthetic fracture or extensor mechanism disruption.[44,45] For these reasons, the discovery of a non-surgical treatment option for established contractures is important.

The findings in this study suggest that local administration of celecoxib improves motion in the stiff knee when compared to the untreated control. This finding is valuable because nearly all in vivo research on arthrofibrosis focuses on the prevention of scar formation – with only a single study looking at the treatment of established contractures.[21] That single study, however, used a rat model for adhesive capsulitis of the shoulder. Interestingly, this study found that the vehicle solution with capsular release showed a less stiff capsule at 24 weeks

compared to the celecoxib treatment group with capsular release. Yet, there was no statistical significance between these two groups. Ultimately, this finding reinforces the observation that celecoxib does not have an additive effect when combined with the capsular release. In fact, the celecoxib treatment group alone had statistically similar stiffness compared to both capsular release groups, suggesting that the drug itself functioned as a proxy capsular release in restoring motion in this model of arthrofibrosis.

In our study, locally delivered celecoxib was superior to a surgical capsular release in this rabbit model of arthrofibrosis. It should be noted that this superior effect was only noted at 24 weeks, and only on static measurements – with no statistical significance in the dynamic stiffness coefficients between the two groups. However, it is notable that celecoxib was at a minimum equivalent, and at best superior, to a capsular release alone. This finding is clinically relevant because for patients who fail conservative treatment for arthrofibrosis, locally delivered celecoxib might offer a less invasive and potentially more effective treatment option to improve joint arc-of-motion. Although consecutive daily IA injections for two weeks may have limited translatability into clinical practice, our findings are promising in pointing future research into the direction of more clinically relevant drug delivery – potentially a single large-dose injection, oral celecoxib, or drug-eluting scaffolds placed near or within joint at time of capsular release.[46]

It is important to discuss the mechanism by which celecoxib attenuated arthrofibrosis in this study. Mechanisms of fibrogenesis are widely discussed in the literature throughout various tissue types.[47] More specifically, and relevant for this study, is the mechanism of fibrosis in tissues specific to the joint space. Several studies point to the activation of periarticular myofibroblasts from mesenchymal stem cells as the primary driver of arthrofibrosis.[2,22-24] Salib et al[25] discussed the ability of celecoxib to prevent arthrofibrosis through the disruption of post-inflammatory cytokines and subsequent interruption of myofibroblast activation. Based on this proposed mechanism, we posit that the celecoxib in our study disrupted the activation of periarticular myofibroblasts from mesenchymal stem cells and interrupted the formation of new scar tissue after the remobilization surgery. Additionally, this study found that intra-articular celecoxib was equivalent to a capsular release. This finding suggests that some reversal of well-established fibrosis occurred with celecoxib equivalent to excision of posterior capsular tissue. Importantly, any speculation on this without molecular or histological data would be conjecture, although this avenue is an important direction for future studies.

Our study has several limitations. Experimentation was constrained by low numbers of rabbits in each experimental group. For budgetary and compassionate reasons with large animal studies, the numbers of rabbits are intentionally kept at the minimum needed to adequately power the study. One rabbit was excluded from all biomechanical analyses in the IA celecoxib group due to a broken K-wire prior to K-wire removal. Additionally, one rabbit from the IA vehicle group, the IA vehicle with capsular release, and the IA celecoxib with capsular release group were each excluded from the capsular release data due to experimental error when running the dynamic load cell device. Despite this experimental attrition, our datasets were sufficiently robust to establish significant differences among relevant treatment groups. We did not complete any histological or genetic data to analyze fibrosis at the cellular and molecular levels, thus precluding augmentation of our findings using established biomarkers. Many previous studies have analyzed histological and molecular data regarding celecoxib treatment as well as capsular release.[28,46] Given that our biomechanical findings are similar to these studies, it is likely that additional phenotyping via histological and molecular approaches would yield similar conclusions. Lastly, the rabbit model of arthrofibrosis is imperfect, as the trauma used on the rabbit joint is exaggerated (i.e. 45° hyperextension of the knee) compared to trauma from human arthroplasty. This exaggerated trauma may induce an unnecessarily severe contracture. However, this model has been carefully validated,[28,30,31,48,49] and is currently the most reliable animal model for arthrofibrosis despite its limitations.

In conclusion, this study found that IA administration of celecoxib significantly improved extension in contracted rabbit knees compared to untreated controls. Additionally, this study found that IA celecoxib was superior to a capsular release in the treatment of arthrofibrosis in a rabbit model. Finally, IA celecoxib combined with a capsular release did not provide additive or synergistic effects in the improvement of extension in the contracted rabbit knee.

Supplementary material

ë An ARRIVE checklist is included to show that the ARRIVE guidelines were adhered to in this study.

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Author information:
- W. H. Trousdale, MD, Orthopedic Surgery Resident
- A. K. Limberg, BS, Research Assistant
- N. Reina, MD, Research Fellow
- C. G. Salib, MD, Research Fellow
- R. Thaler, PhD, Post-Doctoral Scientist
- D. J. Berry, MD, Surgeon
- M. E. Morrey, MD, Surgeon
- J. Sanchez-Sotelo, MD, PhD, Surgeon
- M. P. Abdel, MD, Surgeon
  Department of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota, USA.
- A. Dudakovic, PhD, Research Consultant, Department of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota, USA; Department of Biochemistry & Molecular Biology, Mayo Clinic, Rochester, Minnesota, USA.
- A. van Wijnen, PhD, Research Consultant, Department of Biochemistry, University of Vermont, Burlington, Vermont, USA.