Review Article

The effect of nonsteroidal anti-inflammatory drug use on soft tissue and bone healing in the knee: a systematic review

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Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to mitigate pain and inflammation associated with musculoskeletal conditions; however, there is conflicting data on the adverse effects of these drugs on tissue and bone healing. The objective of this study was to investigate the effect of NSAIDs on the healing of knee, soft tissue, and bone.

Methods: A systematic literature search was conducted across PubMed/MEDLINE, Excerpta Medical Database (Embase)/Ovid, and the Cochrane Central Register of Controlled Trials databases. Clinical, animal, and *in vitro* studies on the effect of NSAIDs on knee healing were included. Risk of bias assessment was performed using the Cochrane bias assessment tool and Methodological Index for Non-Randomized Studies scoring system for included clinical studies, and the Systematic Review Center for Laboratory Animal Experimentation assessment tool for all included animal studies. General study population characteristics, interventions used, NSAIDs utilized, outcome measures, and study results were analyzed using descriptive statistics.

Results: Fifteen articles met the inclusion criteria. Of the 15 studies, there were three clinical, ten animal, and two *in vitro* studies. In clinical studies, nonselective cyclooxygenase (COX) inhibitors and selective COX-2 inhibitors did not cause a significant increase in failure of anterior cruciate ligament (ACL) reconstructions or meniscal repairs with NSAID administration pre-, peri-, or post-operatively in comparison to placebo or no NSAID administration. Among animal studies assessing COX-2 inhibitor effects on soft tissue, healing was impaired (2/4), delayed but unaffected (1/4), or unaffected (1/4). In animal studies assessing COX-1 inhibitors, ligament healing was either increased (1/4), unaffected (2/4), or impaired (1/4). Meanwhile, administration of non-selective COX inhibitors in animals did not affect soft tissue (3/3) and cartilage (1/1) healing. Two *in vitro* studies identified a negative outcome on patellar tendon and ACL cell proliferation or viability after non-selective COX inhibition and variable results after selective COX-2 inhibition.

Conclusions: Animal studies on postoperative NSAID use after knee surgery suggest that administration of selective and nonselective COX-2 inhibitors may impair healing of soft tissue, bone and tendon-to-bone; however, further clinical studies are needed to better characterize dose and duration dependent risks of NSAIDs.

Keywords: Nonsteroidal anti-inflammatory drug (NSAID); cyclooxygenase (COX); knee healing; systematic review

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to mitigate pain and inflammation associated with musculoskeletal conditions. Increased use of NSAIDs has been beneficial in diminishing postoperative opioid use; however, there remains conflicting data on the effect of NSAIDs on soft tissue and bone healing (1-7). NSAIDs function via inhibition of cyclooxygenase (COX), an enzyme responsible for prostaglandin synthesis. There are two isoforms of COX: COX-1 and COX-2. Several in vitro, animal, and clinical studies have identified COX-2 inhibitors to be the primary culprit of causing adverse effects in soft tissue, tendon-to-bone, and bone healing (2,4-6). In the knee, meniscal tissue and intraarticular ligament reconstruction already have limited healing capacity (1). Therefore, there is a need for identifying potential adverse effects in the knee from the perioperative and postoperative use of NSAIDs to avoid decreased or delayed healing and reconstruction graft failure.

The currently available systematic and scoping review articles have taken broader approaches in identifying the effect of NSAID use on tissue healing (2-5,8). However, there is limited information to identify the effect of NSAIDs on tissue healing specifically in the knee, where meniscal repairs, cartilage surgeries and intra-articular ligament reconstructions may be susceptible to delayed or a lack of healing. The purpose of this study was to investigate the effect of NSAIDs on the healing of knee soft tissue and bone. The authors hypothesized that NSAIDs may have a negative effect on soft tissue and tendon-to-bone healing in the knee. We present this article in accordance with the PRISMA reporting checklist (available at https://aoj.amegroups.com/article/view/10.21037/aoj-23-58/rc).

Highlight box

Key findings

- Selective cyclooxygenase (COX)-2 inhibitors may impair soft tissue, bone, and tendon-to-bone healing in the knee of animals.
- Clinically, nonselective and selective COX-2 inhibitors do not impair anterior cruciate ligament and meniscus healing, although with limited evidence.

What is known and what is new?

- Selective COX-2 inhibitors are known to cause adverse effects in overall soft tissue, tendon-to-bone, and bone healing.
- In the knee, selective and nonselective COX-2 inhibitors may impair soft tissue, tendon-to-bone, and bone healing in animals but may not impair healing clinically.

What is the implication, and what should change now?

- Further clinical studies are needed to better understand the dose and duration dependent risks of nonsteroidal anti-inflammatory drugs in knee healing as current literature primarily consists of animal studies.

Methods

This systematic review has been registered to the Prospective Register of Systematic Reviews (PROSPERO ID: CRD42023407331).

Study eligibility

Inclusion criteria for studies included the following: clinical studies investigating tissue healing in the knee after peri- or postoperative NSAID use, animal and *in vitro* studies investigating tissue healing in the knee after NSAID use, published in a peer-reviewed journal, and full English text available.

Exclusion criteria included the following: clinical, animal, and *in vitro* studies not related to knee healing and NSAID use, case reports, reviews, meta-analyses, opinion articles, technique articles, and studies with unavailable English text.

Search strategy

A literature search was conducted across the following electronic databases: PubMed/MEDLINE, Excerpta Medical Database (Embase)/Ovid, and the Cochrane Central Register of Controlled Trials. We developed an inclusive search strategy and conducted a search in August 2022 with no date restrictions employed. The following search strategy was utilized: (((nonsteroidal anti-inflammatory drug OR NSAID) AND (knee OR meniscus

OR ACL OR MCL OR patella OR ligament OR tendon OR muscle OR soft tissue)) AND (healing)). After all articles were collected from the searches, duplicate articles were removed. Title and abstract screening were performed independently by two authors (R.H.S. and J.D.) using the inclusion and exclusion criteria. In studies where both authors agreed on inclusion, full text was reviewed. In cases where consensus was not reached on inclusion of a study, a third author (N.I.K.) evaluated and determined whether the study in question was included.

Risk of bias assessment

All included randomized clinical studies were evaluated for bias using the Cochrane bias assessment tool. All included non-randomized clinical studies were evaluated for bias using the Methodological Index for Non-Randomized Studies (MINORS) scoring system. MINORS is a validated assessment tool for methodological quality of studies by scoring non-comparative (0–16) and comparative studies (0–24), where higher scores indicate lower levels of bias. All included animal studies were evaluated for bias using the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) risk of bias assessment tool. SYRCLE is a validated tool that uses 10 "yes or no" questions, where more "yes" answers indicate lower risk of bias. As there is no validated or consistently utilized risk of bias assessment tool for *in vitro* studies, bias could not be assessed in these studies.

Data extraction

Two authors (R.H.S. and J.D.) extracted and validated all collected data from each included study. For clinical and animal studies, the data points collected included the number of subjects, sex, mean age, mean follow-up, type of pathology, procedure or intervention performed (if any), type of NSAID administered, NSAID dosage, timing of drug use, outcome measures, control group, and study results. For *in vitro* studies, the tested specimen, type of NSAID tested, outcome measures, and study results were collected. The type of NSAID administered was categorized as either selective COX-1, selective COX-2, or nonselective COX inhibitors. Selective inhibitors have preferential blockade of either the respective COX-1 or COX-2 enzyme. Nonselective inhibitors act on both COX enzymes to a significant degree without preferential blockade of either enzyme.

Statistical analysis

All statistical analyses were performed using Excel (Microsoft Corp, Redmond, WA, USA). All extracted data were analyzed using descriptive statistics, including weighted mean values and frequencies, due to the heterogeneity of reported data. Weighted mean values were calculated based on the sample size reported in each included study.

Results

On initial search, a total of 617 articles were identified. After deduplication, 539 articles were screened based on title and abstract, of which 504 were excluded according to the inclusion and exclusion criteria. After full text analysis of 33 articles, studies were excluded due to the wrong intervention (n=5), injury location (n=8), or study design (n=5). We identified 15 articles for inclusion in our study (*Figure 1*).

Clinical studies

We identified three clinical studies assessing the use of NSAIDs on primarily anterior cruciate ligament (ACL) reconstructions and to a lesser extent on meniscal repairs across 8,009 patients (4,638 male, 3,371 female) (9-11). The weighted mean age of patients was 28.8 years with an average follow-up of 24.5 months (*Table 1*). The procedures studied included isolated ACL reconstruction (7,902/8,009) (9,11), isolated meniscus repair (64/8,009) (10), and combined meniscus repair and ACL reconstruction (43/8,009) (9-11).

One study assessed selective COX-2 inhibitors (9), one study assessed a nonselective inhibitor (10), and one study assessed both selective COX-2 and nonselective COX inhibitors (11). None of the included studies found a significant increase in failure of each procedure with NSAID administration pre-, peri-, or post-operatively in comparison to placebo or no NSAID administration. Ge *et al.* found no significant difference in knee stability and subjective outcomes when comparing post-operative NSAID versus opiate administration after ACL reconstruction (9). The clinical study results are summarized in *Table 2*.

Animal studies

Ten animal studies investigated the effect of NSAIDS on

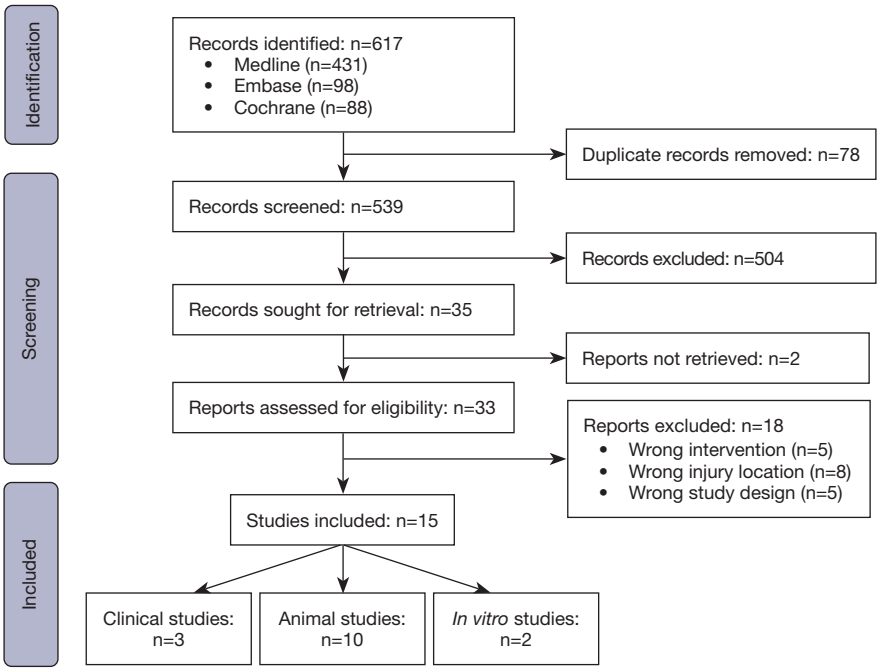

Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of the article selection process.

Table 1 Patient demographics in clinical studies assessing NSAID effects on post-operative knee outcomes

Study (LOE)	Number of patients (male/female)	Mean age, years	Mean follow-up, months
Ge *et al*. (III) (9)	80 (56/24)	28	12
Proffen *et al*. (III) (10)	107 (45/62)	15	66
Soreide *et al*. (III) (11)	7,822 (4,537/3,285)	29	24

NSAID, nonsteroidal anti-inflammatory drug; LOE, level of evidence.

Table 2 The effect of NSAIDs on post-operative knee outcomes

Study	Type of pathology	Intervention	NSAID administered [COX-selectivity]*	Dosage	Primary outcome measures	Secondary outcome measure(s)	Control group	Result
Ge *et al.* (9)	ACL tear (100%), meniscal tear (34%)	ACL reconstruction	Celecoxib [2]	200 mg twice a day post-operatively	Knee stability	IKDC, Lysholm score, Tegner scale	Opioid	No significant difference
Proffen *et al.* (10)	Meniscal tear (100%), ACL tear (40%)	Meniscal repair +/–ACL reconstruction	Keterolac (non-selective)	7.5–60 mg based on body weight peri-operatively	Reoperation, failure of meniscal repair	KOOS, SF-36 Health Survey, IKDC	No NSAID	No significant difference
Soreide *et al.* (11)	ACL tear (100%), meniscal tear (46%)	ACL reconstruction	Diclofenac [2], keterolac (non-selective), celecoxib [2], other	Not reported	Graft survival	KOOS-QOL score	No NSAID	No significant difference

*, Selective inhibitors have preferential blockade of either the respective COX-1 (referred to as 1) or COX-2 (referred to as 2) enzyme. Nonselective inhibitors act on both COX enzymes to a significant degree without preferential blockade of either enzyme (referred to as non-selective). NSAIDs, nonsteroidal anti-inflammatory drugs; COX, cyclooxygenase; ACL, anterior cruciate ligament; IKDC, International Knee Documentation Committee Subjective Knee Form; KOOS-QOL, Knee Injury and Osteoarthritis Outcome Score-Quality of Life; SF-36, Short Form-36 Health Survey.

Table 3 General characteristics of animal studies assessing NSAID effects on knee healing

Study	Number of animals (male/female)	Strain (failure load)†	Animal type (body weight)*	Dosage (mg/kg)	Length of follow-up
Bogatov *et al.* (12)	80 (M)	21–55 N/kg	Rats (592 g)	Low dose: 10.6 High dose: 28.1	2 weeks
Dahners *et al.* (13)	140 (M)	28–52 N/kg	Rats (450 g)	5	2 weeks
Elder *et al.* (14)	50 (M)	21–53 N/kg	Rats (515 g)	5–30	2 weeks
Ferry *et al.* (15)	215 (F)	52–72 N	Rats (425 g)	2.5–60	2 weeks
Hanson *et al.* (16)	150 (F)	37–48 N/kg	Rats (430 g)	2.5–60	2 weeks
Moorman *et al.* (17)	24 (F)	24–115 N	Rabbits (NR)	70	4 weeks
Sauerschnig *et al.* (18)	32 (F)	28–69 N	Rabbits (3.5 kg)	10	3 weeks
Taroni *et al.* (19)	16 (F)	NA	Dogs (40 kg)	NR	6 months
Warden *et al.* (20)	60 (F)	13–35 N	Rats (275 g)	5	12 weeks
Watson *et al.* (21)	18 (M)	NA	Rabbits (4.25 kg)	2.1–3	70 days

†, strain was applied at a constant rate of 0.25 mm/s for all studies that assessed load to failure and is expressed as a range. *, Body weight is expressed as an average value. NSAID, nonsteroidal anti-inflammatory drug; M, male; F, female; NR, not reported; NA, not assessed.

knee healing across 785 animals (288 male, 497 female) (12-21). All animals included in each study were skeletally mature. The mean follow-up time ranged from 0.5–6 months. General study characteristics are summarized in *Table 3*. The primary knee injuries studied were medial collateral ligament (MCL) transections (504/785). Eight studies investigated soft tissue healing and two studies assessed bone healing. Seven studies did not use any repair intervention and allowed for MCL healing via scarring (12-14,16,17,20,21). Six studies assessed COX-2 inhibitors (14-16,18-20), four studies assessed COX-1 inhibitors (12,13,15,16), and four studies assessed non-selective COX inhibitors (*Table 4*) (15-17,21).

Among studies assessing COX-2 inhibitor effects on soft tissue, healing was impaired (2/4) (14,15), delayed but unaffected (1/4) (20), or unaffected (1/4) (16). For bone healing, Taroni *et al.* noted delayed but unaffected tibial osteotomy healing after administration of a COX-2 inhibitor, while Sauerschnig *et al.* noted a decrease in tendon-to-bone healing in ACL reconstruction tunnels (18,19). In studies assessing COX-1 inhibitors, ligament healing after transection was either increased (1/4) (16), unaffected (2/4) (12,13), or impaired (1/4) (15). After administration of nonselective COX inhibitors, soft tissue (3/3) (15-17) and cartilage (1/1) (21) healing were unaffected in all studies.

In vitro studies

Two *in vitro* studies investigating the effect of NSAIDs on knee specimens through cell testing were identified (22,23). Both studies identified a negative outcome on cell proliferation or viability after nonselective COX inhibition. Riley *et al.* identified no negative outcome on patellar tendon cell proliferation from selective COX-2 inhibition (22); however, Schwarting *et al.* found reduced cell viability among ACL 3T3 cell lines (23). The *in vitro* study results are summarized in *Table 5*.

Risk of bias assessment

Three non-randomized comparative clinical studies were assessed using the MINORS scoring system and were determined to have a low risk of bias (Table S1) (9-11). The ten included animal studies were evaluated using the SYRCLE risk of bias assessment tool (12-21). Nine of these animal studies were determined to have a low risk of bias and one was determined to have an unclear risk of bias (Table S2).

Discussion

The most important finding of the present study was that nonselective and selective COX-2 inhibitor administration among patients who underwent ACL reconstruction and

Table 4 The effect of NSAIDs on knee healing in animals

Study	Type of pathology	Intervention	NSAID administered [COX-selectivity]	Primary outcome measure	Control group	Result
Bogatov *et al.* (12)	MCL transection	Allowed to heal via scarring	SC-560 [1]	Failure load	Placebo	Unaffected strength of healing ligament
						Increased strength of contralateral ligament
Dahners *et al.* (13)	MCL transection	Allowed to heal via scarring	Piroxicam [1]	Failure load	Placebo	Increased early strength of healing ligament but final strength unaffected
						Unaffected strength of uninjured ligaments
Elder *et al.* (14)	MCL transection	Allowed to heal via scarring	Celecoxib [2]	Failure load	Placebo	Decreased strength of healing ligament
						Unaffected strength of uninjured ligaments
Ferry *et al.* (15)	Patellar tendon transection	Stabilization of patella with cerclage suture	Ibuprofen [non-selective], naproxen [non-selective], piroxicam [1], celecoxib [2], valdecoxib [2]	Failure load	Placebo	Unaffected strength of healing tendon for ibuprofen and naproxen but decreased with piroxicam, celecoxib, and valdecoxib
						Unaffected strength of uninjured limbs
Hanson *et al.* (16)	MCL transection	Allowed to heal via scarring	Naproxen [non-selective], piroxicam [1], rofecoxib [2]	Failure load	Placebo	Increased strength of healing ligament for piroxicam and unaffected with naproxen and rofecoxib
						Unaffected strength of uninjured limbs
Moorman *et al.* (17)	MCL transection	Allowed to heal via scarring	Ibuprofen [non-selective]	Failure load	Placebo	Unaffected strength of healing tendon
						Unaffected strength of uninjured ligaments
Sauerschnig *et al.* (18)	ACL resection	ACL reconstruction	Celecoxib [2]	PGE2 in synovium; bone formation	Placebo	Decreased tendon-to-bone healing
Taroni *et al.* (19)	Cranial cruciate ligament rupture	Tibial plateau osteotomy	Firocoxib [2]	Bone healing	Intra-articular MSCs	Decreased early healing but final clinical scores unaffected
Warden *et al.* (20)	MCL transection	Allowed to heal via scarring	Celecoxib [2]	Failure load	Placebo	Decreased early healing but final strength unaffected
Watson *et al.* (21)	Knee arthrosis	Allowed to heal via scarring	Indomethacin [non-selective]	Microscopic findings	No NSAID	Unaffected healing of cartilage but fewer granules over chondrocytes

NSAIDs, nonsteroidal anti-inflammatory drugs; COX, cyclooxygenase; MCL, medial collateral ligament; ACL, anterior cruciate ligament; PGE2, prostaglandin E2; MSCs, mesenchymal stromal cells.

Table 5 *In vitro* study characteristics and the effect of NSAIDs on knee specimen

Study	Specimen	NSAID tested [COX-selectivity]	Dosage	Primary outcome measure	Result
Riley *et al*. (22)	Patellar tendon	Indomethacin [non-selective], naproxen [non-selective], diclofenac [2], aceclofenac [2]	Indomethacin: 20 μg/mL Naproxen: 100 μg/mL Diclofenac: 2 μg/mL Aceclofenac: 10 μg/mL	Tendon cell proliferation	Indomethacin and naproxen inhibited cell proliferation, while diclofenac and aceclofenac had no significant effect
Schwarting *et al*. (23)	ACL MC3T3 and 3T3 cell lines	Ibuprofen [non-selective], parecoxib [2]	Ibuprofen: 5–100 μM Parecoxib: 5–100 μM	Cell viability	Both ibuprofen and parecoxib reduced cell viability

NSAIDs, nonsteroidal anti-inflammatory drugs; COX, cyclooxygenase; ACL, anterior cruciate ligament.

meniscus repair did not affect postoperative stability, subjective outcomes, and either ACL graft failure or meniscal healing. Among animal studies on postoperative NSAID use after knee surgery, it was reported that administration of selective and nonselective COX-2 inhibitors may impair healing of extra-articular soft tissue, bone and tendon-to-bone.

Limited clinical studies currently exist in assessing the effects of NSAIDs on knee, soft tissue, and bone healing. While only three clinical studies were identified in our systematic review, these studies identified no significant differences in postoperative stability, subjective outcomes, and either ACL graft failure or meniscal healing between the NSAID recipients and control groups (9-11). Similar clinical studies assessing NSAID use after rotator cuff repair have caused concern specifically for selective COX-2 inhibitor use. Oh *et al.* reported postoperative use of selective COX-2 inhibitors increased the rate of rotator cuff retear compared to nonselective COX inhibitors (24). However, the failure rate was relatively higher for large rotator cuff repairs and should not be directly compared with the different physiologic environment of the knee (25-27). This difference could perhaps be attributed to the difference in environment between the ACL (intra-articular) and the rotator cuff insertions (mostly extra-articular/subacromial).

The animal studies included in this systematic review had greater variability in healing outcomes compared to the clinical studies. Nonselective COX inhibitors were found to not affect soft tissue and cartilage healing across studies (15-17,21). Selective COX-1 inhibitors were found to either improve or not affect ligament healing in three studies assessing MCL transection models, while one study by Ferry *et al.* found a negative effect on patellar tendon healing (12,13,15,21). Four articles found that soft tissue healing after selective COX-2 inhibitor use was either impaired, delayed, or unaffected (14-16,20). It is worth noting that male rats were used in the study by Elder *et al.* to investigate healing after selective COX-2 inhibitor use (14). Male rats are known to have a quick metabolism for two COX-2 inhibitors in particular: rofecoxib and celecoxib (28,29). The quick metabolism of male rats for COX-2 inhibitors may apply to other NSAIDs, making the use of female rats preferable. The half-life of COX-2 inhibitors is more comparable between female rats and humans (29,30). However, the medication dosages given to animals must be adequately adjusted to assess impaired healing, because small animals tend to have a higher metabolism than humans. In a study on the effects of perioperative parecoxib use on tibial shaft fracture healing, Hjorthaug *et al.* utilized allometric scaling based on calorific demand to determine parecoxib dosages in rats and allow for an adequate comparison to humans; an increase in dosage by a factor of four was required in the rat models (31).

In regard to healing of bone and intra-articular structures, dose duration and location of the structure of interest seems to be of great importance. Sauerschnig *et al.* reported impaired tendon-to-bone healing after ACL reconstruction in rabbits, suggesting that ACL graft healing in reconstruction tunnels may be compromised or delayed with selective COX-2 inhibitor use (18). However, these conclusions are not wholly defended by their data. They were able to demonstrate notable intra-articular prostaglandin E2 (PGE2) differences amongst control and COX-2 cohorts, however, they were unable to demonstrate any notable difference between intra-articular characteristics of the soft tissue portion of the grafts at 3 or 6 weeks between control groups and COX-2 administered groups. Further, the changes in bone density and new bone

formation seem to be attributed to PGE2 levels. However, they found PGE2 levels rebounded to normal or elevated levels after cessation of COX-2 inhibitor administration, thereby suggesting that bone healing is restored when treatment is concluded. This is consistent with prior literature by Taroni *et al.* who found COX-2 inhibitor administration can lead to delayed but ultimately unimpaired bony healing in tibial osteotomies (19).

Another interesting finding by Saurschnig *et al.* was that delayed bony healing seemed to be different based upon location, with less bone formation in the midsection of the tunnel when compared to the aperture, meaning the bone nearest to the intra-articular space was less impaired (18). This is similar to prior literature which has shown the negative effect of COX inhibitors on bone healing, primarily in diaphyseal fractures with no effect in the metaphysis (32,33). Also furthering the argument of treatment duration being an additional variable of importance, an animal study on diaphyseal tibia fracture healing in rats demonstrated no negative effect of immediate or delayed short-term administration of parecoxib, a selective COX-2 inhibitor (31). These findings may be applicable to the clinical setting, regarding both the healing of diaphyseal fractures and soft tissue knee structures.

Both *in vitro* studies on the effect of nonselective and selective COX-2 inhibitors on patellar tendon and ACL cell lines identified decreased cell proliferation and viability (22,23). It is unclear if the reduced cell proliferation and viability identified in these studies would translate to delayed or impaired healing in a clinical model. Nonetheless, these studies provide insight into potential mechanisms for delayed and impaired healing caused by COX inhibitors that were identified in animal studies.

There were some limitations to our study. The number of clinical studies identified in our search were limited, with animal studies comprising the majority of included articles. While all the clinical studies assessed administration of NSAIDs in patients who underwent ACL reconstruction and/or meniscus repair, the animal studies assessed healing of the knee after transection of the MCL, ACL reconstruction, or patellar tendon repair. The transection model in animals makes for a different physiologic environment for healing than the clinical studies assessing surgical reconstruction. Additionally, medication dosage, duration, and average study follow-up time varied across studies. Lastly, a meta-analysis was not possible due to the heterogeneous presentation of the data.

Conclusions

Animal studies on postoperative NSAID use after knee surgery suggest that administration of selective and nonselective COX-2 inhibitors may impair healing; however, clinical studies demonstrated no detrimental effects on meniscal sutures and ACL reconstructions. Further clinical studies are needed to better characterize dose and duration dependent risks.

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Footnote

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Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Methodological Index for Non-Randomized Studies (MINORS) scoring for included comparative clinical studies

Study	Clearly stated aim	Inclusion of consecutive patients	Prospective data collection	Endpoints appropriate to study aim	Unbiased assessment of study endpoint	Follow-up period appropriate to study aim	Loss to follow-up less than 5%	Prospective calculation of the study size	Adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analysis	Total score
Ge *et al.* (2018) (9)	2	2	2	2	0	2	2	0	1	2	2	2	19
Proffen *et al.* (2014) (10)	2	2	2	2	0	2	2	0	2	2	2	2	20
Soreide *et al.* (2016) (11)	1	2	2	2	0	2	2	2	2	2	2	2	21

The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score is 24 for each comparative study.

Table S2 Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) risk of bias assessment for included animal studies

Study	Selection bias			Performance bias		Detection bias		Reporting bias	Attrition bias	Other sources of bias	Overall risk of bias
	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding	Random outcome assessment	Blinding	Incomplete outcome data	Selective outcome reporting		
Bogatov *et al.* (2003) (12)	+	+	+	+	?	?	–	+	+	+	Low
Dahners *et al.* (1988) (13)	+	+	+	?	?	?	?	+	+	+	Low
Elder *et al.* (2001) (14)	?	+	?	?	?	?	?	+	+	+	Unclear
Ferry *et al.* (2007) (15)	+	+	+	?	–	+	–	+	+	+	Low
Hanson *et al.* (2005) (16)	+	+	+	?	–	?	–	+	+	+	Low
Moorman *et al.* (1999) (17)	+	+	+	+	?	?	?	+	+	+	Low
Sauerschnig *et al.* (2018) (18)	+	+	+	?	–	+	–	+	+	+	Low
Taroni *et al.* (2017) (19)	+	+	+	+	+	+	+	+	+	+	Low
Warden *et al.* (2006) (20)	+	+	+	+	–	+	–	+	+	+	Low
Watson *et al.* (1976) (21)	+	+	+	+	?	?	?	+	+	+	Low

"+" indicates low risk of bias; "?" indicates unclear risk of bias; "–" indicates high risk of bias.

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