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Injectable Ketorolac and Corticosteroid Use in Athletes: A Systematic Review

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Injectable Ketorolac and Corticosteroid Use in Athletes: A Systematic Review

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Context: The use of injectable medications to help athletes quickly return to the field of play after injury is common. Understanding the effects and risks of these medications will help providers make informed decisions regarding their use in this patient population.

Objective: To evaluate the utilization, efficacy, and adverse effects of injectable ketorolac and corticosteroids in athletes.

Data Sources: This systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A systematic search of the literature was performed using multiple databases (PubMed, Embase, Cochrane, Web of Science, and ClinicalTrials.gov). Secondary references were appraised for relevant articles. No randomized controlled trials or other prospective studies were identified. Articles included retrospective database reviews and physician survey studies.

Study Selection: A total of 6 studies met the inclusion and exclusion criteria and were reviewed by 2 independent reviewers with a third consulted in the case of disagreement, which was not needed.

Study Design: Systematic review.

Level of Evidence: Level 5.

Data Extraction: Two reviewers recorded rate of use, effectiveness of treatment, and reported side effect data.

Results: Most studies centered around the football athlete, either professional or collegiate. Professional football game day use of intramuscular ketorolac declined from 93.3% (28/30) in 2002 to 48% in 2016. Collegiate football game day use of intramuscular ketorolac declined from 62% in 2008 to 26% in 2016. Game day corticosteroid injection was far lower than ketorolac usage. Both medications were reported to be effective with few adverse events.

Conclusion: Use of injectable ketorolac is common but declining in professional and college football. Pain control efficacy is good, and risk of adverse events is low. The incidence of injectable corticosteroid use in athletes is unknown. Use of injectable corticosteroids in athletes allows for early return to sport activities with no reported complications.

Keywords: injection; ketorolac; corticosteroids; athlete

Musculoskeletal injuries account for a significant pain burden worldwide. The World Health Organization ranks musculoskeletal injuries as the number one cause for long-term pain.[2] In sport, musculoskeletal pain can vary widely among athletes, resulting in moments of inaction or entire games missed. Musculoskeletal injuries specific to muscle fibers are often less severe, but chronic, and can be prone to reinjury when inadequately managed. Ekstrand et al[9] found that muscle-specific injuries, strains, and contusions accounted for nearly one-third of all injuries experienced in professional soccer players over 8 years. Over 92% of those injuries were confined to the lower limb, many of which were classified as reinjury or aggravation of a nonhealed injury.[9]

A major problem faced by today's team physician is managing muscular injuries and associated pain. Multiple treatment modalities are available, but the efficacy of each has been questioned. The most common modalities utilized for pain management include a combination of PRICE (protection, rest, ice, compression, elevation), oral nonsteroidal anti-inflammatories (NSAIDs), oral corticosteroids, intramuscular (IM) injections for general pain relief, and corticosteroids injected directly into the injured tissue. All modalities available

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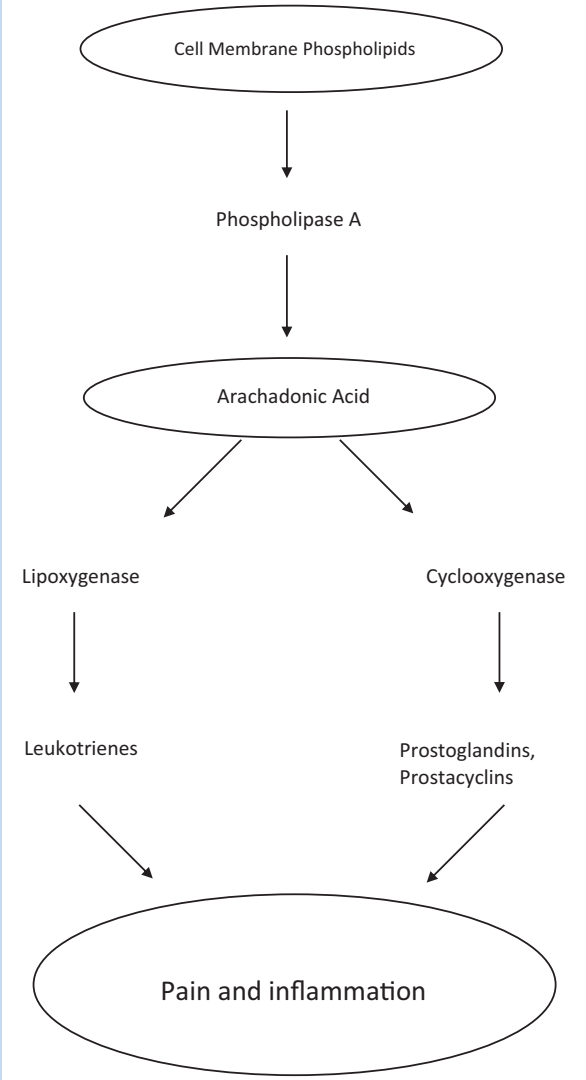

Figure 1. Breakdown of cell membrane phospholipids through the lipoxygenase and cyclooxygenase pathways, leading to pain and inflammation.

to the sports physician attempt to address the natural response of the body when dealing with an injury, with the goal of returning the athlete to full participation in the least amount of time and with the lowest risk for reinjury.

When muscle is injured, damage extends to the cellular level and cell membranes lyse, spilling their contents into the local tissue and bloodstream, initiating the inflammatory cascade. Phospholipids from lysed cellular membranes are broken down to arachidonic acid (AA), the primary building block of all inflammatory biomarkers (Figure 1). AA is broken down via either the lipoxygenase pathway or the cyclooxygenase (COX) pathway. The former pathway leads to the production of leukotrienes, compounds that act locally to increase vascular permeability and facilitate chemotaxis of leukocytes to the area of injury. The COX pathway is further differentiated into 2 pathways: COX-1 and COX-2. COX-1 is a constitutional pathway that is always active in certain organ systems. COX-1 is responsible for mucous production in the gut, temperature maintenance in homeostasis, and preservation of kidney function by maintaining dilation of the afferent arterioles in the nephron. COX-2 is inducible and the primary target for pain management for the physician. The COX-2 pathway produces prostaglandins, prostacyclin, and thromboxane, substrates that further recruit inflammatory cells, increase vascular permeability, sensitize local nociceptive fibers, and assist in clotting.

NSAIDs primarily function as inhibitors of the COX pathways. Most NSAIDs indiscriminately block COX-1 and COX-2. By inhibiting the COX pathways, they work to prevent pain and inflammation by reducing prostaglandin sensitization of peripheral nociceptors and reducing vascular permeability by reducing prostacyclin production.[20] The inflammatory response to muscle injury, however, is a crucial component of healing despite the associated pain and discomfort. The natural healing process can take days to weeks and requires several overlapping steps related to cellular migration, proliferation, and tissue remodeling. Each step involves a highly coordinated incursion of leukocytes that are recruited by the products of the COX and lipoxygenase pathways. A single administration of IM ketorolac in injured rat muscle was shown to reduce the concentration of 277 proteins, 14 of which had previously been documented as integral to muscle injury repair.[1]

Oral corticosteroids are considered the most powerful anti-inflammatories in any physician's toolkit.[20] Oral and injectable corticosteroids inhibit both the lipoxygenase and COX pathways. They prevent leukocytes from adhering to vascular structures, thus preventing the diapedesis that allows these inflammatory cells to congregate at sites of injury. For many years, sports physicians have used injectable corticosteroids to help injured athletes return to the field of play quickly. The World Anti-Doping Agency (WADA) has banned corticosteroid use (IM, intravenous [IV], oral, or rectal) in competitive play, unless a Therapeutic Use Exemption (TUE) form is provided by a physician noting their necessity.[4,35] In recent years, ketorolac has become the sport physician's injectable medication of choice to help athletes return to the field after injury.

This systematic review aims to evaluate the utilization, efficacy, and adverse effects of injectable ketorolac and corticosteroids in athletes.

METHODS

This systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[17] A systematic search of the literature was performed using PubMed, Embase, Cochrane, and Web of Science databases for studies published between January 1, 2000, and October 16, 2019. A search for current studies using ClinicalTrials.gov was also performed. The reference lists of any

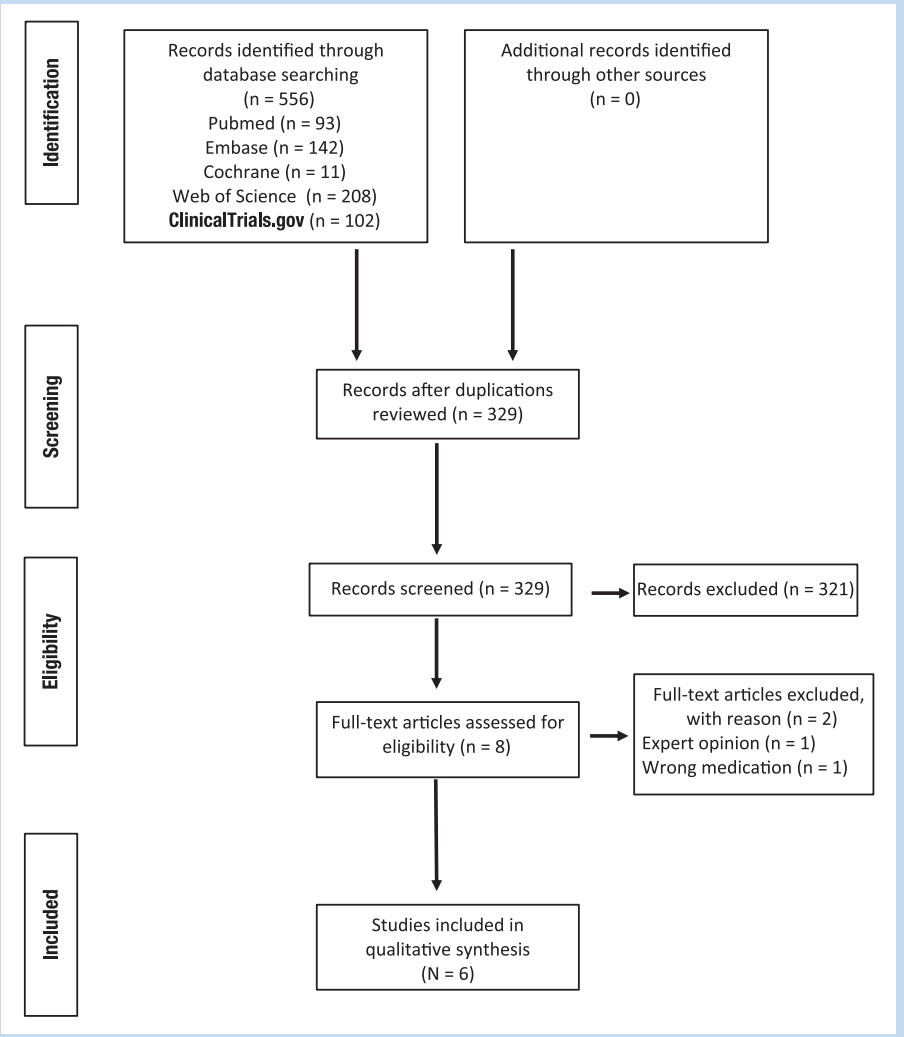

Figure 2. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart of article assessment from initial selection to final inclusion.

relevant systematic reviews and articles were manually checked for relevant articles, and Google Scholar was utilized as a secondary source. Keywords and Medical Subject Headings terms were used separately and in combination in the search; individually, these terms included *injections* OR *inject, ketorolac* OR *Toradol* OR *anti-inflammatory agent, non-steroidal* OR *corticosteroid,* AND *athlete* OR *sport* OR *game* OR *athletic injuries* OR *sports medicine*. Articles were screened using information from titles and abstracts, and the following inclusion criteria were applied: published in English in a peer-reviewed journal, was specific to the use of the injectable medication (either ketorolac or corticosteroid) in athletes, and presented new data on the topic. Studies were excluded if they were review articles, animal studies, studies of chronic musculoskeletal conditions, or studies of the general population.

No prospective studies were identified in the literature review. With the identified studies being retrospective reviews of limited patient populations and physician surveys, methodological quality was rated as low. Studies were reviewed for data on utilization, discussion of pain relief and ability to return to play after injection, and discussion of adverse effects encountered with the use of the injectable forms of ketorolac and corticosteroids. Multiple forms of bias are possible in retrospective reviews and physician surveys including collection bias, observation bias, recall bias, and reporting bias.

RESULTS

Of 8 articles identified,[5,7,13,22,23,26,28,31] 2 were excluded due to 1 being expert opinion[22] and the other utilizing medications other than ketorolac or corticosteroids.[23] Thus, 6 studies met the inclusion and exclusion criteria (Figure 2). When reviewing individual studies for inclusion/exclusion, the 2 primary reviewers were successful in achieving consensus, and no

additional reviewer was needed. During screening of abstracts and titles, the most common reasons for exclusion included review article, chronic musculoskeletal condition, nonathlete population, or medication other than ketorolac or corticosteroid.

Study Characteristics

Identified studies were published between 2000 and 2018, with 4 physician surveys,[5,26,28,31] 1 retrospective review of a multiteam injury database,[13] and 1 retrospective review of medical records from a single team.[7] Five of the studies included only male football athletes.[5,7,13,28,31] One study included athletes from a variety of sports and both male and female participants.[26] Ages were not specifically reported, but 4 studies included only National Football League (NFL) athletes[7,13,28,31] and 1 study only collegiate athletes.[5] A single survey study included questions about athletes as young as 15 years old.[26]

Utilization of Injectable Ketorolac and Corticosteroids in Athletes

There were no prospective reports on the use of injectable ketorolac in athletes. In 2002, of 30 NFL teams responding to a survey on game day use of ketorolac, 93.3% (28/30) reported game day usage of IM ketorolac, with an average of 15 players per team receiving an injection in the hours before kickoff.[31] Most of the teams reported they would administer IM ketorolac up to once a week for players during the season.[31] A survey of NFL head orthopaedic team physicians in 2008 showed that this percentage was unchanged, and 79% of physicians would administer 5 or more injections prior to each game.[28] By 2016, this number had dropped to 48% of physicians administering game day ketorolac, with 28% administering 5 or more injections per game.[28] Utilization among National Collegiate Athletic Association Division I football head orthopaedic team physicians showed a similar decline, decreasing from 62% of physicians reporting game day usage in 2008 to 26% in 2016.[5] A survey of the memberships of the American Medical Society for Sports Medicine (AMSSM) and the American Orthopaedic Society for Sports Medicine (AOSSM) in 2012 revealed that nearly half of the 1100 responding physicians used IM ketorolac in treatment of athletes.[26] Nonsurgical sports medicine physicians (AMSSM members) were more likely to use ketorolac in general (orally or IM) compared with their surgical counterparts and were also more likely to use IM ketorolac. Of the physicians who used ketorolac, 79% used the medication in the collegiate athlete population and 42.9% used it in the professional athlete, and 53.7% of respondents listed 15 years old as the minimum age at which they would consider pregame ketorolac injection.[26] Of respondents, 71% used injectable ketorolac in both male and female athletes.[26]

There were also no prospective studies on the use of game day corticosteroid injections in athletes, but the utilization of game day corticosteroid injection appears to be far lower than ketorolac usage. A retrospective review of 13 years of NFL data reported only 58 corticosteroid injections directly into the injury region of acute hamstring strain. The majority of these athletes received their injection less than 72 hours after injury.[13] A report on the use of corticosteroid injection for a variety of muscle strain and ligament sprain injuries in a single NFL team over a period of 3 seasons revealed a total of 38 injections in 31 athletes.[7]

Effectiveness of Injectable Ketorolac and Corticosteroids in Athletes

Effectiveness of injectable ketorolac and corticosteroids in athletes was only reported in 4 studies.[7,13,26,31] In 2000, most NFL head team physicians felt a single ketorolac injection alleviated 50% to 75% of a player's pain and lasted 1 to 2 days. Because of this, most staff (24/27 [89%]) stated that they would give ketorolac up to once a week during the season.[31] In the survey of AMSSM/AOSSM members, 50% of respondents believed that ketorolac injection improved function, while 38.3% thought it accelerated the return to activities.[26] Each injection was perceived to be efficacious for less than 24 hours.[26]

Corticosteroid injection treatment also appears effective. When used in the treatment of hamstring strain in NFL players, 49 players (84.5%) missed no game time, 8 players missed 1 game, and 1 player missed 2 games.[13] Overall treatment of these athletes still averaged 24 days (range, 6-65 days).[13] When considering corticosteroid injection for treatment of a variety of injuries, Drakos et al[7] reported that all players were able to return to play at some time after their injection (mean, 10.4 days), with 55% of players not missing a single game. Athletes injected for quadriceps strains missed an average of 4 games (mean, 36.5 days), and those injected for hamstring strains missed an average of 3 games (mean, 28 days).[7]

Adverse Effects of Injectable Ketorolac and Corticosteroids in Athletes

Only 4 of the identified studies mentioned adverse events from the use of game day injection treatment in athletes.[7,13,26,31] Reports of adverse effects from game day ketorolac injection in athletes are low. In the NFL, only 6 adverse events were reported over a single season. These included 4 isolated muscle injuries, 1 gastrointestinal disturbance, and 1 instance of next-day postinjection soreness. Several teams expressed concern about psychological dependence by players, but this was not studied further.[31] AMSSM/AOSSM members reported local skin reaction (5%), bleeding (2.9%), and kidney problems (1.9%) as the most common adverse events, but the severity of these events was not described. Of respondents, 88% reported no adverse events.[26] No minor or major adverse events were reported with the use of game day corticosteroid injection,[7,13] specifically, no infections, no major re-aggravation of hamstring injury, and no muscle rupture.[13]

DISCUSSION

The purpose of this systematic review is to evaluate the utilization, efficacy, and adverse effects of injectable ketorolac and corticosteroids in athletes. With no prospective studies

regarding the use of these injectable medications in this patient population, the report quality is low. All identified studies were either retrospective reviews[7,13] or physician surveys,[5,26,28,31] and the majority focused only on male professional football players,[7,13,28,31] with 1 study focusing on collegiate male football players,[5] and 1 considering all sports and both male and female participants.[26]

Oral NSAID use is a mainstay of treating musculoskeletal injuries in athletes. Oral NSAIDs such as ibuprofen and naproxen are widely used by athletes. Ziltener et al[36] surveyed college athletes and found that 29% reported routinely taking NSAIDs immediately prior to match play. That same group found that NSAIDs were reportedly useful for some muscle injuries but not others. Athletes reported improvement in symptoms for injuries, such as contusions and delayed-onset muscle soreness, but not strains.[36]

Ketorolac is currently the only Food and Drug Administration (FDA)–approved injectable NSAID medication. Since FDA approval in 1989, ketorolac has become a favored medication for game day pain relief in athletes. The IM and IV formulations have a more rapid onset of action than many traditional oral NSAIDs, reaching therapeutic plasma levels in less than 10 minutes.[26] It is a highly charged compound with 99% of the compound bound to albumin in plasma.[25] With such rapid onset and a half-life of roughly 6.5 hours, coupled with a low cost, it has ideal anti-inflammatory properties with regard to pain management and cost. Also available in oral (per os [PO]) and intranasal formulations, ketorolac has shown good pain relief efficacy regardless of route of administration.[3] The absorption, onset of action, and duration of effect between the injectable and PO forms are quite similar. The excellent PO absorption stems partially due to 99% protein binding once absorbed via the gut.[3,19] Onset to analgesic effect of the IM formulation is approximately 30 minutes and between 30 and 60 minutes for PO. Both IM and PO offer approximately 4 to 6 hours of pain relief. Even cost has little variation between formulations. Interestingly, the analgesic effect is capped at 10 mg, with studies showing no additional benefit above that dosage. Based on the evidence available, for athletes who require pain management on the sideline, PO ketorolac would be justified over IM due to equivocal bioavailability and efficacy, without the risk associated with injections.

Emergency department data comparing IM ketorolac, PO ibuprofen, and both IM/PO placebos for mild to moderate musculoskeletal pain found that the analgesic effect was not statistically different.[32] The same study found no significant difference in time to analgesic effect. Another double-blinded study compared efficacy of varying doses for IM ketorolac for moderate to severe pain in an emergency department setting found no statistically significant improvement in pain scores with doses above 10 mg of IM ketorolac.[18] No studies were found that specifically compared PO and IM ketorolac for analgesic effect on muscular injuries.

Ketorolac slows muscle healing by indiscriminate reversible inhibition of COX-1 and COX-2.[3,10] While short-term analgesia is a desired effect and is not typically detrimental to overall healing because of the reversible nature of the medication, acute and chronic use of ketorolac can suppress the body's natural course of tissue repair and lead to poor healing.[1] In athletes, chronic ketorolac use may theoretically increase thresholds for pain during rehabilitation, while at the same time cause delayed healing and subsequently greater risk of reinjury of suboptimally healed muscle. In rat models with induced eccentric muscle contraction injuries, researchers have repeatedly been able to prove, with statistical significance, that injection with ketorolac leads to decreased torque generation in the injured muscles. This reduction in strength was shown with repeated consistency when testing was performed over the course of both days and weeks.[29]

Side effects of ketorolac are similar to other NSAIDs that work by inhibiting the COX pathway. Adverse effects include dyspepsia, gastrointestinal bleeding/ulceration, renal dysfunction, and reduction in platelet function and blood clotting. Extended use of parenteral ketorolac at higher doses increases the risk of gastrointestinal side effects (20%) and renal impairment.[8] NSAIDs should be avoided in individuals with coexisting gastric disorders.[24] Additionally, increasing the dose of ketorolac beyond a daily maximum of 40 mg in adults does not provide improved efficacy, but will increase the risk of developing serious adverse events.[14]

NSAIDs should also be avoided in athletes with a history of baseline renal disease. Healthy adults experience transient decreases in renal blood flow and glomerular filtration rate while on a salt-restricted diet.[34] NSAID use in healthy individuals who were renally stressed with dehydration, exercise, and heat exposure demonstrated a small but significant drop in glomerular filtration rate compared with acetaminophen and placebo.[11] This can be compared in the setting of salt-depleted athletes while competing/participating in sport.

Ketorolac decreases platelet aggregation and thromboxane production, increasing the potential to cause bleeding.[27] This is an important consideration in contact/collision sports due to risk of injury to the brain, liver, spleen, and kidneys. Systemic side effects of ketorolac must be considered as well, including headache, asthma, and a negative effect on fracture healing. Mehallo et al[16] identified practical management guidelines through the basis of animal models and limited human studies. Specifically, NSAIDs should be avoided in the treatment of completed fractures, stress fractures at higher risk of nonunion, or in the setting of chronic muscle injury.[16] In experimental animal models, COX-2 inhibitors have been shown to have less gastrointestinal side effects compared with their other NSAID counterparts. However, the same study also demonstrated detriments to tissue-level repair. Specifically, they have been shown to impair mechanical strength return after acute injury to bone, ligament, and tendon.[33]

Table 1. Recommendations from the NFL Physician Society task force on the use of ketorolac in the NFL that are more specific to the NFL (and general sports medicine) patient population

1	Ketorolac should not be used prophylactically as a means of reducing anticipated pain either during or after participation in NFL games or practices.
2	Ketorolac use should be limited to those players diagnosed with an injury or condition and listed on the teams' latest injury report or after a physician diagnosed injury or condition that occurs after the last injury report has been submitted to the NFL prior to competition.
3	Ketorolac should be given in its oral preparation under typical circumstances, as it is recognized that the oral preparation (1) has faster onset of action on the IM preparation, (2) has a duration of action that is equivalent to the IM and IV forms, and (3) has a plasma concentration-time curve that is nearly identical to the IM and IV preparations.
4	IM and IV injection of ketorolac should not be used except *after* an acute, game-related injury where significant visceral or central nervous system bleeding is not expected and where other oral or IM pain medications are inadequate or not tolerated. If IM or IV ketorolac is felt to be appropriate by the treating physician, the lowest possible dose should be used.

IM, intramuscular; IV, intravenous; NFL, National Football League.

A task force appointed by the NFL Physician Society published recommendations on the use of ketorolac in the NFL in 2012.[15] There were 8 primary recommendations listed. Some of these recommendations are common to the use of any NSAID medication (in athletes and the general patient population): The medication should only be administered under the direct supervision and order of a team physician; it should be given in the lowest effective dose; it should not be given with other NSAIDs; and it should not be taken by players with a history of allergic reaction to ketorolac or other NSAIDs, in a player with renal compromise, or a player with a history of prior adverse reaction to ketorolac or other NSAIDs. Recommendations more specific to the use of ketorolac in NFL athletes are listed in Table 1.

Contraindications to corticosteroid injections include injecting near a localized infection, injecting at a fracture site, or injecting areas at high risk for tendon rupture. Potential side effects include postinjection pain flare, soft tissue and subcutaneous fat atrophy, skin hypopigmentation, and, most significantly in the athlete, tendon or ligament weakening or rupture.[21] Of the listed complications, excluding pain, skin atrophy (2.4%) and skin hypopigmentation (0.8%) are the most frequently noted complications. Fat atrophy and skin hypopigmentation are more likely to occur with superficial injection sites, possibly due to overinfiltration of medication into the subcutaneous tissues. Soft tissue changes may occur anywhere from 6 to 12 weeks after injection.[12] There are numerous case reports of tendon rupture after corticosteroid injection, with plantar fascia and Achilles tendon the most commonly reported ruptures.[20,21]

Route of administration of medication is an important consideration regardless of the material being used, as a potential for adverse events exists during any injection procedure. Infection, bleeding, and postinjection neuritis have been reported. Complications can be prevented with strict adherence to aseptic techniques and being familiar with the local anatomy of the injection site.[6] There are no prospective studies reporting on adverse events from the use of IM ketorolac in athletes.

Ethical Considerations

Being a physician in the world of athletics has unique ethical challenges. Balancing the interests of athletes, coaches, families, school administrators, team owners, and agents is often difficult. The primary ethical issue that must be addressed is "first do no harm." As stated by Testoni et al,[30] the use of injections is controversial and poses an important ethical dilemma. Is it ethical to assist someone in masking their pain simply so they can compete in a sporting event when participation may lead to even greater injury? Could delaying recovery of muscular injuries with NSAIDs cause more harm than benefit? Furthermore, the decision-making process for underaged athletes in the high school or college setting may complicate the situation as more individuals are involved. The use of local anesthetic injections in athletes is not considered performance-enhancing[22] and is not banned by WADA, and the use of corticosteroids may be allowed through the TUE process.[35] However, the use of these injections has its own set of possible side effects and complications. The ultimate outcome of reducing pain and maximizing performance are mixed. A retrospective study conducted on professional rugby players in Australia demonstrated that performance between players injected and not injected with a local anesthetic was not substantially different.[23] The complexities of short-term gains for an athlete who chooses to stay on the field by limiting pain and

enabling maximum performance are enormous. Thus, it is crucial for the team physician to work with the athlete to make an informed decision.

CONCLUSION

The current systematic review reveals that pregame IM ketorolac injections are commonly used by professional and collegiate football team physicians with good efficacy and limited side effects. The use of injectable ketorolac in this patient population is declining. The incidence of game day corticosteroid injection use by team physicians is unknown. There is evidence that use of injectable corticosteroids may lead to early return to play with no adverse events. Game day injections of ketorolac and corticosteroids, and the use of oral NSAIDs are common in sports medicine. Injection of ketorolac and use of oral NSAIDs have potential to decrease pain and inflammation in the setting of a musculoskeletal injury; however, use of such medications carries risks for the athlete, including gastrointestinal side effects, renal dysfunction, bleeding, and delayed healing. Because oral NSAIDs have rapid onset of action, similar duration of action and equal pain relieving efficacy as IM ketorolac, the possible adverse effects of the injection procedure can be avoided altogether by utilizing oral preparations when pregame analgesia is desired. Because of the recognized increased bleeding risk, the use of NSAIDs should be handled carefully in the setting of collision sports. Ethical concerns of when to use such medications may prove difficult, as many medical and social factors may affect one's decision. Finally, with the continued, significant use of pregame IM ketorolac for pain management at the collegiate and professional levels, it is time for the sports medicine community to prospectively study its use and report on both the positive and the negative outcomes encountered.

REFERENCES

1. Bryant A, Aldape MJ, Bayer CR, et al. Effects of delayed NSAID administration after experimental eccentric contraction injury—a cellular and proteomics study. *PLoS One*. 2017;12:e0172486.
2. Bubnov R, Yevseenko V, Semeniv I. Ultrasound guided injections of platelet rich plasma for muscle injury in professional athletes. Comparative study. *Med Ultrasound*. 2013;15:101-105.
3. Buckley M, Brogden R. Ketorolac: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. *Drugs*. 1990;90:86-109.
4. Campbell RS, Dunn AJ. Radiological interventions for soft tissue injuries in sport. *Br J Radiol*. 2012;85:1186-1193.
5. Carver TJ, Schrock JB, Kraeutler MJ, McCarty EC. The evolving treatment patterns of NCAA Division I football players by orthopaedic team physicians over the past decade, 2008-2016. *Sports Health*. 2018;10:234-243.
6. Cheng J, Abdi S. Complications of joint, tendon, and muscle injections. *Tech Reg Anesth Pain Manage*. 2007;11:141-147.
7. Drakos M, Birmingham P, Delos D, et al. Corticosteroid and anesthetic injections for muscle strains and ligament sprains in the NFL. *HSS J*. 2014;10:136-142.
8. Dugowson C, Gnanashanmugam P. Nonsteroidal anti-inflammatory drugs. *Phys Med Rehabil Clin N Am*. 2006;17:345-354.
9. Ekstrand J, Roos H, Tropp H. Normal course of events amongst Swedish soccer players: an 8-year follow-up study. *Br J Sports Med*. 1990;24:117-119.
10. Eming S, Martin P, Tomic-Canid M. Wound repair and regeneration: mechanisms, signaling, and translation. *Sci Transl Med*. 2014;6:265SR6.
11. Farquhar WB. Effects of acetaminophen and ibuprofen on renal function in the stressed kidney. *J Appl Physiol*. 1999;86:598-604.
12. Kumar N, Newman RJ. Complications of intra- and peri-articular steroid injections. *Br J Gen Pract*. 1999;49:465-466.
13. Levine WN, Bergfeld JA, Tessendorf W, Moorman CT. Intramuscular corticosteroid injection for hamstring injuries: a 13-year experience in the National Football League. *Am J Sports Med*. 2000;28:297-300.
14. Matava MJ. Injectable nonsteroidal anti-inflammatory drugs in sport. *Clin J Sport Med*. 2018;8:443-450.
15. Matava M, Brater DC, Gitter N, et al. Recommendations of the National Football League Physician Society Task Force on the use of Toradol® ketorolac in the National Football League. *Sports Health*. 2012:4:377-383.
16. Mehallo CJ, Drezner JA, Bytomski JR. Practical management: nonsteroidal antiinflammatory drug (NSAID) use in athletic injuries. *Clin J Sport Med*. 2006;16:170-174.
17. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *Int J Surg*. 2010;8:336-341.
18. Motov S, Yasavolian M, Likourezos MA, et al. Comparison of intravenous ketorolac at three single-dose regimens for treating acute pain in the emergency department: a randomized controlled trial. *Ann Emerg Med*. 2017;70:177-184.
19. Mroszczak EJ, Jung D, Yee J, Bynum L, Sevelius H, Massey I. Ketorolac tromethamine pharmacokinetics and metabolism after intravenous, intramuscular, and oral administration in humans and animals. *Pharmacotherapy*. 1990;10(pt 2)33S-39S.
20. Nepple JJ, Matava MJ. Soft tissue injections in the athlete. *Sports Health*. 2009;1:396-404.
21. Nichols AW. Complications associated with the use of corticosteroids in the treatment of athletic injuries. *Clin J Sport Med*. 2005;15:370-375.
22. Orchard JW. Long-term safety of using local anesthetic injections in professional rugby league. *Am J Sports Med*. 2010;38:2259-2266.
23. Orchard JW. Benefits and risks of using local anesthetic for pain relief to allow early return to play in professional football. *Br J Sports Med*. 2002;36:209-213.
24. Paoloni JA, Orchard JW. The use of therapeutic medications for soft-tissue injuries in sports medicine. *Med J Aust*. 2005;183:384-388.
25. Powell E, Tokish JM, Hawkins RJ. Toradol use in the athletic population. *Curr Sports Med Rep*. 2002;1:191.
26. Sawyer GA, Anderson BD, Raukar NP, Fadale PD. Intramuscular ketorolac injections in the athlete. *Sports Health*. 2012;4:319-327.
27. Schafer AI. Effects of nonsteroidal anti-inflammatory therapy on platelets. *Am J Med*. 1999;106(5B):25S-36S.
28. Schrock JB, Carver TJ, Kraeutler MJ, McCarty EC. Evolving treatment patterns of NFL players by orthopaedic team physicians over the past decade, 2008-2016. *Sports Health*. 2018;10:453-461.
29. Suzuki KP, Bremner SN, Minamoto, VB, et al. Intramuscular ketorolac tromethamine acutely impairs skeletal muscle function after eccentric injury. 55th Annual Meeting of the Orthopaedic Research Society, Poster No. 405. 2009.
30. Testoni D, Hornik CP, Smith PB, Benjamin DK Jr, McKinney RE Jr. Sports medicine and ethics. *Am J Bioethics*. 2013;13:4-12.
31. Tokish JM, Powell ET, Schlegel TF, Hawkins RJ. Ketorolac use in the National Football League—prevalence, efficacy, and adverse effects. *Phys Sportsmed*. 2002;30:19-24.
32. Turturro MA, Paris PM, Seaberg DC. Intramuscular ketorolac versus oral ibuprofen in acute muscuskeletal pain. *Ann Emerg Med*. 1995;26:117-120.
33. Warden SJ. Cyclo-oxygenase-2 inhibitors: beneficial or detrimental for athletes with acute musculoskeletal injuries? *Sports Med*. 2005;35:271-283.
34. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. *Am J Med*. 1999;106:13S-24S.
35. World Anti-Doping Agency. *The World Anti-Doping Code International Standard: Prohibited List*. World Anti-Doping Agency; 2020.
36. Ziltener JL, Leal S, Fournier PE. Non-steroidal anti-inflammatory drugs for athletes: an update. *Ann Phys Rehabil Med*. 2010;53:278-288.