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Review Article

Intraarticular Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in the Treatment of Inflammatory Arthritis: Establishing a Role in Arthritis Patient Care Today

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Abstract

Inflammatory arthritis is very commonly encountered in clinical practice and is on the rise due to inflammatory osteoarthritis (OA) and gouty arthritis from an aging population (inflamaging) and increasing prevalence of metabolic syndrome. Common therapeutic options used to manage the pain and inflammation includes oral non-steroidal anti-inflammatory drugs (NSAIDs), oral steroids, intramuscular (IM) NSAIDs and intraarticular (IA) steroid injections. Due to the limitations of IA steroids, the use of IA NSAIDs represents a useful therapeutic alternative in many patients with inflammatory arthritis, especially in those who recur after IA steroids or failed to respond to oral NSAIDs or IA steroids. However, many rheumatologists and orthopaedic surgeons, especially in my country, are still not aware of the therapeutic efficacy and role of IA NSAIDs. In this review, I summarised the currently available clinical and experimental publications and studies concerning IA NSAIDs, including my own clinical experience and studies. The administration of IA NSAIDs discussed will cover IA ketorolac, IA oxicams and IA parecoxib. Pertinent case examples to illustrate how IA NSAIDs can play an important role in our daily management of patients with inflammatory arthritis will be given.

Keywords: *Inflammatory; Arthritis; Intraarticular; NSAIDs; Ketorolac; Piroxicam; Parecoxib*

Introduction

Inflammatory arthritis is very commonly encountered in clinical practice and is seen in various settings including inflammatory osteoarthritis (OA), gouty arthritis, rheumatoid arthritis, spondyloarthritis, reactive arthritis and post-arthroplasty synovitis. Common therapeutic options used to manage the pain and inflammation includes oral NSAIDs, oral steroids, intramuscular (IM) NSAIDs and intraarticular (IA) steroid injections. Each option is subjected to its limitations and side effects, including gastric intolerance with oral NSAIDs and IA steroids [1]. And in many Asians arthritis patients who have poorly controlled diabetes, IA steroids may be a relative contraindication as it can cause a transient hyperglycaemia episode.

The use of IA NSAIDs represents a useful therapeutic alternative in many patients with inflammatory arthritis. However, many rheumatologists and orthopedic surgeons, especially in my country, are still not aware of the therapeutic efficacy and role of IA NSAIDs. In this review, I would like to present the currently available clinical and experimental publications and studies concerning IA NSAIDs, including my personal clinical experience and studies. The administration of IA NSAIDs will cover IA ketorolac, where there have been the most number of studies published, IA parecoxib, IA piroxicam and IA tenoxicam and IA lornicam. I will be using pertinent case examples to illustrate how IA NSAIDs can play an important role in our daily management of patients with inflammatory arthritis.

Why intra-articular NSAIDs injection? The clinical need

In my clinical practice, I often encountered patients with persistent or recurrent knee pain despite IA steroid injections, which is the first line treatment for inflammatory arthritis. In 2014, I began to enquire whether IA NSAIDs, beginning with IA ketorolac, would have a role in the treatment of such patients with recurrent or persistent joint synovitis. Ketorolac has been shown to be an effective and safe parental NSAID [2-4]. Hence, being a patient-oriented and solution-oriented physician and rheumatologist, I did some research into IA NSAID injections for the treatment of inflammatory arthritis and concluded that there is strong scientific and clinical evidence for the usage of IA NSAIDs.

Illustrative case example 1

AKH, 75/CHI/F with chronic left knee pain, worsened after fall 3 months ago, resulting to left knee effusion. Ultrasound of the left knee showed Effusion 3+, Synovitis 2+ and Osteophytes (Figure 1 and 2). Left knee aspiration was done and IA ketorolac 30 mg was given. She was reviewed a week later and the left knee pain improved. Follow-up viscosupplementation with IA hyaluronic acid (HA) Orthovisc was given.

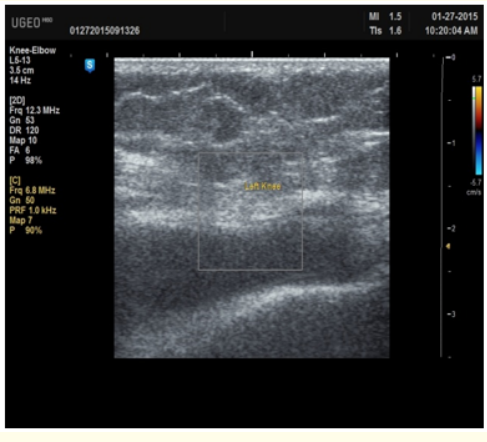

Figure 1: *Ultrasound Left Knee-Effusion.*

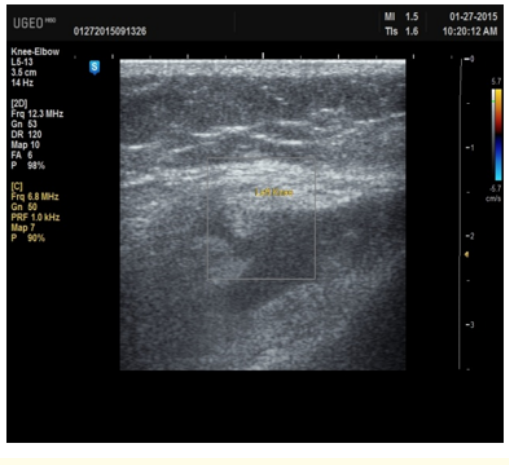

Figure 2: *Ultrasound Left Knee-Synovitis.*

Although IA steroids have been the traditional and established treatment for inflammatory arthritis because of its potent anti-inflammatory effects, there have been some recent concerns about the chondrotoxicity of repeated long-term usage of IA steroid injections into the joints. Initial studies showed long term steroid injections over a 2-year period to be safe, but subsequent studies showed cartilage volume loss in patients who had repeated triamcinolone injections on MRI follow-up over 2 years [5,6]. Different steroids have different effects on the chondrocytes in experimental studies and while methylprednisolone affects the chondrocytes cellular viability, ketorolac does not [7,8]. Hence, the potential role of IA NSAIDs in the management of inflammatory may increase in the future.

Experimental studies of intra-articular NSAIDs joint injection

There have been several studies done in rats model of induced osteoarthritis with IA ketorolac, piroxicam and parecoxib, the first and only cyclooxygenase-2 (COX-2) inhibitor available and IA ketorolac and lornoxicam in the rabbit knee joint.

The use of I/A ketorolac has been studied in animal models and shown to have no detrimental effects on the joints [9,10]. The local tolerability of lornoxicam after single and repeated IA administration into the rabbit knee joint did not show signs of toxicity to the bone or chondrotoxicity [11].

Su., *et al*. in their study also showed the safety of repeated I/A ketorolac and Hyaluronic Acid (HA) injections over a 4-week period [12]. There were no pharmacokinetics interaction or toxicity seen. This was also confirmed by a similar study using IA piroxicam in the rats OA model [13].

In terms of efficacy, IA piroxicam administration showed significant reduction in the rat knee swelling, corresponding to the reduction of prostaglandin E2 levels in the joint. Both IM and IA piroxicam led to rapid rise in the plasma piroxicam concentration, but the systemic bioavailability of piroxicam was relatively lower compared to that after IM injection, indicating that the IA route provided a higher piroxicam concentration in the local tissue [13]. Hence the therapeutic effect of IA administration was more effective in terms of reduction in joint swelling and inflammatory levels compared to IM route. In the study with IA parecoxib, the excitatory amino acids levels were significantly reduced and they were accompanied with suppression of synovial inflammation and a significant inhibition of cartilage degeneration in the anterior cruciate ligament-transected knee in rats [14].

And in the studies where IA NSAIDs were combined with HA administration, there were no pharmacokinetic interactions, but on the other hand, the anti-inflammatory and anti-nociceptive efficacies of IA piroxicam were synergistically increased upon co-treatment with HA in the rat OA knee model [15].

The positive experimental studies have underlined the basis of the good outcome experience that have been seen in clinical practice. When administered locally, high concentrations of NSAIDs can be achieved at the site of cell injury with a better outcome and local administration can lead to clinical benefits such as use of lower doses, lower subsequent systemic exposure and a reduced frequency of adverse events [16].

Intra-articular ketorolac joint injection in clinical practice

Ketorolac, as an injectable non-narcotic analgesic, has been widely reported first in 1990, being effective for moderate-to severe pain from post-surgical settings to renal colic and is as effective as morphine and had prolonged analgesic efficacy after a single dose, with a good safety profile, even in the elderly patients [1-3].

IA ketorolac was first reported by Reuben., *et al*. in 1995, 14 years ago, for post-operative pain relief following outpatient knee arthroscopy [17]. The group who received a combination of IA bupivacaine and IA ketorolac had decreased postoperative pain, a decreased need for postoperative analgesics and an increased analgesic duration. Since then, there has been several reported studies where IA ketorolac has been used as part of regional anesthesia for knee surgery in ACL reconstruction and gave superior analgesic control. And in arthroscopic knee surgery, IA ketorolac enhances the analgesic efficacy of local anesthetics and reduced the use of systemic analgesics with its concomitant side-effects avoided, as shown in several studies [18-23]. Probably though local anti-inflammatory and metabolic effects, IA ketorolac provided better pain control and less dependence on opioid analgesics [24].

The study by Proffen., *et al*. confirmed that there was no deleterious effect of IA ketorolac on musculoskeletal healing following arthroscopic meniscus repair and that it could be used to harness its benefits of decreased narcotic requirement, decreased pain and shorter length of hospital stay without negatively influencing the long-term outcome of the surgery [25].

In the setting of total knee replacement, IA ketorolac has been used successfully as part of a local pain control measure and avoiding the complications of epidural anesthesia and nerve blocks that are often used in the regional anesthesia for pain control [26-28]. Also the studies showed that the usage of IA ketorolac enabled patients to have better post knee arthroplasty recovery and walking distance.

In the setting of knee osteoarthritis, when IA ketorolac was combined with IA Hyaluronic Acid (HA) for OA knee, there was a more rapid analgesic onset than IA HA alone without any adverse effects [29-30].

Having gathered enough evidence for the efficacy of IA ketorolac we did our own clinical study in January 2015 looking at the first 40 patients who had IA ketorolac injection and this presentation was made at the 49th Singapore-Malaysia Congress of Medicine Meeting that was held in Singapore in 2015 [31]. More than 75% of the patients had been previously treated with IA steroids or failed oral NSAIDS. The response rate was 90% and there were no adverse events from the IA ketorolac.

Following our clinical study, there have been several publications substantiating the role and efficacy of IA ketorolac in shoulder conditions, hip arthritis and other joints as well besides the several publications elucidated to earlier on knee arthritis and surgery.

In the setting of shoulder arthritis, there are at least 5 publications related to the efficacy of IA ketorolac. Intra-articular ketorolac has been shown to have superior post-surgical pain relief when combined with morphine and ropivacaine and improved patient satisfaction [32,33]. In another study, IA ketorolac was found to be superior to triamcinolone injection in patients with shoulder impingement syndrome [34]. To add support to the usage of IA ketorolac, there were another 2 publications from our Asian colleagues confirming the effectiveness of IA ketorolac. Akhtar., *et al*. from Pakistan showed that in the management of adhesive capsulitis, showing that IA ketorolac was better than I/A HA in reduction of pain [35]. Xu., *et al*. from China demonstrated in their study that adding ketorolac to intra-articular analgesia was a safe and effective method to improve pain relief after shoulder arthroscopy [36].

In the study on hip osteoarthritis, IA ketorolac was as effective as IA corticosteroid, with a good safety profile [37]. In another recent study, IA ketorolac combined with hyaluronic acid injection for osteoarthritis of the thumb was better than HA alone, with a more rapid onset of analgesic action [38].

In conclusion, there is a definite clinical role for IA ketorolac in management of the painful knee joint as alluded by the various publications, including my own clinical experiences. Over 25 publications have been summarized demonstrating that IA ketorolac as a safe and effective therapeutic tool with good analgesic and anti-inflammatory efficacy.

Intraarticular oxicam NSAIDs in the treatment of inflammatory arthritis

There have been several clinical studies with IA oxicams, in particular IA piroxicam and tenoxicam. The advantage of oxicams being the long elimination half life of up to 70 hours, with the exception of lornoxicam which has a short half life of 3 - 4 hours [39].

The analgesic efficacy was shown in 2 studies where IA piroxicam was used in the setting of post-knee arthroscopy and both studies showed that the patients receiving IA piroxicam had lower pain scores and analgesic demand and no side effects. The analgesic efficacy was most evident in the patients who have preoperative joint inflammation [40,41].

We did over own clinical study with IA piroxicam in 60 patients with inflammatory arthritis [42]. 72 joints were injected with IA piroxicam and there was a 79.5% improvement rate and no adverse events were recorded. 2 brief patient examples are given for illustrative purposes.

Illustrative case example 2

G D, 54/Ind/F with Inflammatory OA knees for 1 year and a history of Naproxen allergy presented with bilateral knee pain and swelling. Ultrasound showed Effusion+, Synovitis 2+, Osteophytes (Figure 3). She was given IA piroxicam to the left knee with 60% reduction

of the pain and followed-up IA HA Orthovisc combined with piroxicam (2nd dose) was given with further improvement. She had IA beta-methasone on the right knee followed by IA piroxicam and HA Orthovisc. She had a good outcome at 2 months follow-up. No AE was noted.

IA tenoxicam was also studied in post-arthroscopic knee surgery analgesia with good efficacy and high patient satisfaction and could be safely combined with bupivacaine, as in the other previously mentioned IA ketorolac studies [43]. In a similar study involving IA lornoxicam in patients undergoing arthroscopic anterior cruciate ligament reconstruction, the combination of intraarticular ropivacaine, morphine and lornoxicam was superior to control or to a combination of ropivacaine and morphine [44]. An interesting study of IA lornoxicam in patients with RA, showed that weekly IA injections for 3 weeks relieved inflammatory knee pain and reduced synovitis and effusion on serial ultrasound [45]. We concur with this experience in our RA patients with IA piroxicam.

Illustrative patient example 3

SL, 57/Ind/F with a h/o rheumatoid arthritis had Right knee pain and swelling for 1 month duration. Ultrasound of the knees showed Synovitis 1+, Power Doppler +ve (Figure 3). IA piroxicam 20mg was given was completely resolution of the pain for 1 month on follow-up.

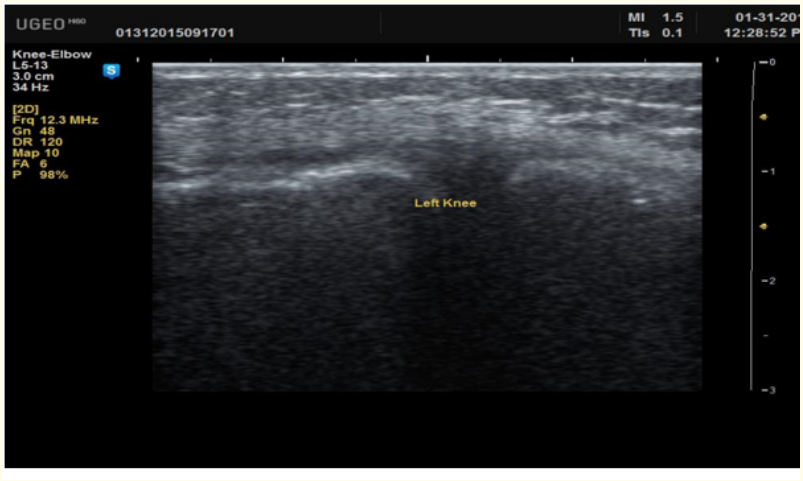

Figure 3: *Ultrasound of the knee with RA showing synovitis.*

Intraarticular parecoxib in the treatment of inflammatory arthritis

Parecoxib (Dynastat) is the only parental COX-2 Selective NSAID available in the market and developed by Pfizer [46]. Parecoxib, a water soluble prodrug of the oral formulation of valdecoxib, is approximately 20,000fold more potent against COX-2 than COX-1. It is the first and only injectable COX-2 inhibitor available. It is rapidly metabolized into the active form, with peak plasma valdecoxib concentration occurring between 30min and 3.5 hour**.** Intramuscular (IM) parecoxib has been shown in several studies to be superior in analgesic efficacy when compared with IM diclofenac and morphine, having a faster onset of action and a longer duration of effect. In the study comparing diclofenac and parecoxib given pre-emptively in the setting of general surgery, those given parecoxib had 100% total pain relief up to 12 hours compared to none in the diclofenac group [47].

Being a COX-2 selective NSAID, parecoxib has less gastric and renal side effects. The adverse event rates of 10% was I to placebo [48]. The efficacy of this drug has been well studied in several reports and in various settings including orthopaedic hip, spine and knee surgery [49]. Parental parecoxib was associated with a significantly improved pain relief without an increase in adverse effects and many of the studies were done in Asian patients [50-54]. In my clinical practice, I have used parecoxib without any cross-reactivity in patients who were allergic to conventional non-COX-2 selective NSAIDs.

The recently published pooled analysis of 28 trials and 10-year post-authorization data has conclusively shown a good efficacy and safety profile [55]. Hence, the good results obtained can be extrapolated to the clinical setting for the treatment of moderate-to-severe arthritis pain with IA parecoxib.

We were the first to present the clinical efficacy and safety of IA parecoxib at the Australian Rheumatology Associations 57th Annual Scientific Meeting Poster, 2016. We reported our initial experience with 60 Asian patients using intra-articular injection of cyclooxygenase-2 inhibitor parecoxib in the treatment of inflammatory arthritis [56].

In our patient group, IA parecoxib was used alone in 62% of the patients, while in the remaining 38% of the patients, IA parecoxib was combined with HA and/or steroids. 30% had complete resolution of the joint inflammation while 70% had improvement.

I present a patient example of the efficacy of IA parecoxib in a patient with recurrent knee inflammation due to gouty arthritis.

Illustrative patient example 4

RBD, a 37-year-old Malay man, who has a history of recurrent gouty knee arthritis since 2011. He had previous treatment with intra-articular steroids injections in 2014 every 2 - 3 months. In 2015, he had recurrent knee inflammation since Jan, for which IA prednisolone and IA brufencon were given in Jan and March. Uric Acid level was high at 11.3 mg/dl despite febuxostat. He had persistent knee pain and required IA ketolorac 30 mg and IA piroxicam 20 mg injection. Ultrasound of Right knee showed effusion 3+ and synovitis 2+ and aspiration of 30 mls fluid done. IA piroxicam 20mg and betasol 1 ml were given. He had left knee pain and swelling 1 week later and had similar knee aspiration and injection done (Figure 4 and 5).

2 weeks later in May 2015, he had similar attacks of knee inflammation for which IA parecoxib 40 mg were given to both knees. He had weekly IA parecoxib 40 mg injections into both knees for 3 weeks until the knee synovitis and effusion subsided. For the 2nd half of the year, he required an additional 3 more injections of IA parecoxib injections for control of his gouty flares due to noncompliance and dietary indiscretion.

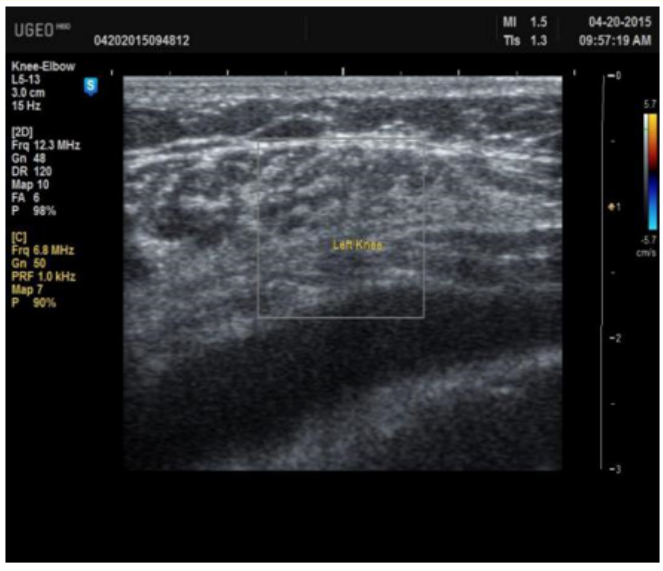

Figure 4: *Ultrasound showing left knee effusion*

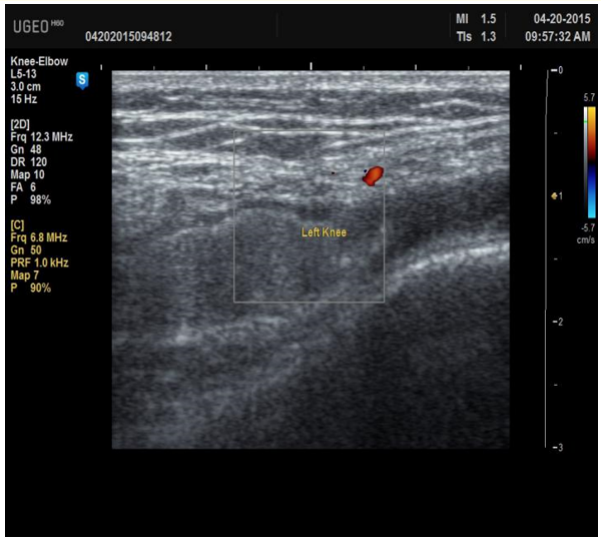

Figure 5: *Left knee synovitis and tophi. Power doppler +ve.*

Synovitis following total knee replacement is not uncommonly encountered in clinical practice. We were the first to report the successful usage of IA parecoxib to treat the inflammatory arthritis following total knee arthroplasty in 8 Asian patients [57].

Our findings were echoed by our Chinese colleagues who reported similar superior outcomes with IA parecoxib in the treatment of early knee OA compared with oral celecoxib and these were accompanied by a reduction in synovial fluid proinflammatory cytokines IL-6 and TNF-alpha and an increase in the concentration of the anti-inflammatory factor IL-10 [58].

Can intra-articular NSAIDs be used in combination with steroids or hyaluronic acid injections?

Yes. Several experimental studies have shown the synergistic effect of IA NSAIDs (piroxicam and ketorolac) with IA HA, without any pharmacokinetic interactions. Lee., *et al*. were the first to report the rapid analgesic onset of IA HA plus ketorolac in OA knee [29]. In the setting of inflammatory OA, I routinely combine IA NSAIDs with HA, as reported in the studies earlier with IA ketorolac, IA piroxicam and IA parecoxib, with a good outcome [31,42,56]. In the 3 studies eluded to earlier, I have given successfully IA piroxicam combined with HA in 38 patients, IA ketorolac together with HA in 22 patients and IA parecoxib combined with HA in 23 patients, a total of 83 patients reported. In the ultrasound-guided hip injection case series, there were 2 patients who had IA parecoxib together HA Hyglan GF-20 and 3 patients with IA piroxicam combined HA with good outcomes [59].

For patients with severe joint effusions, usually the knees, I have safely used the combination of IA NSAIDs and steroids. In the 3 series that I have reported, there were a total of 41 patients successfully treated with this IA combination. We were the first to report this clinical success. In an experimental study on the *in vitro* anti-inflammatory effects of ketorolac and methylprednisolone, ketorolac showed a 1.4 - 2.5 fold reduction in cellular inflammation markers (E-selectin, vascular cell adhesion molecule and human leukocyte antigen DR) over the control while methylprednisolone showed a 2.1 to 5.8-fold reduction [60]. While there has not been any studies on the synergistic anti-inflammatory effects of NSAIDs and steroids, there may be possible mechanistic synergy as steroids inhibits the phospholipase A2 while NSAIDs inhibit the cyclo-oxygenase enzyme inside the inflamed joint. Hence in selected cases of severe inflammatory arthritis, IA combination of steroids and NSAIDs may be used.

When to use Intra-articular NSAIDs in clinical practice

After reviewing the various studies and also from our clinical experience with IA NSAIDs usage over the last 4 years, I propose that IA NSAIDs can be used in selected patients with the following clinical scenarios:

1. Recurrent synovitis
2. Severe arthritis with severe pain
3. Recurrent joint inflammation despite I/A steroids
4. In patients when I/A steroids is relatively contraindicated
5. Patients who refuses IA steroid injections for fear of side-effects and chondrotoxicity
6. Severe joint effusions
7. Post-TKR synovitis [61,62]
8. Post-arthroscopic surgery
9. Combined with IA HA in inflammatory OA.

Conclusion

In this review, I have given a comprehensive summary of the experimental and clinical basis for IA NSAIDs and their efficacy and usefulness in the treatment of inflammation arthritis and also post-surgical knee pain. IA NSAIDs has demonstrated good efficacy in a variety of clinical settings, especially in inflammatory OA and even RA. IA NSAIDs is an additional armamentarium available that we as clinicians managing patients daily with arthritis pain can use to effectively control inflammatory joint pain with a rapid onset of action and minimal adverse effects. Patients can be relieved of their debilitating joint pain with a single IA NSAID injection due to immediate local on-site action and drug retention rather than having to take a long course of oral NSAIDs or analgesics and avoid the side effects of prolonged oral NSAIDs ingestion. In addition, there is no fear of chondrotoxicity with IA NSAIDs and on the other hand, the inhibition of inflammatory prostaglandins by IA NSAIDs may be chondroprotective. Furthermore IA NSAIDs are readily available and inexpensive and can be safety combined with IA HA with synergistic efficacy. In the light of all these advantages, I propose that IA NSAIDs be utilised as a first or second line IA anti-inflammatory agent for the effective treatment of the painful inflamed joints.

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Bibliography

1. Bellamy N., *et al*. "Intraarticular corticosteroid for treatment of osteoarthritis of the knee". *Cochrane Database of Systematic Reviews* 19.2 (2006:): CD005328.
2. Kenny GNC. "Ketorolac Trometamol-A New Non-Opoid Analgesic". *British Journal of Anaesthesia* 65.4 (1990): 445-446.
3. Kinsella J., *et al.* "Ketorolac Trometamol for postoperative analgesia after orthopaedic surgery". British Journal of Anaesthesia 69.1 (1992): 19-22.
4. Smallman JMB., *et al*. "Ketorolac for postoperative analgesia in elderly patients". *Anaethesia* 47.2 (1992): 149-152.
5. Raynauld JP., *et al*. "Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial". *Arthritis and Rheumatology* 48.2 (2003): 370-377.
6. McAlindon TE., *et al*. "Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients with Knee Osteoarthritis: A Randomized Clinical Trial". *The Journal of the American Medical Association* 317.19 (2017): 1967-1975.
7. Wernecke C., *et al*. "The effect of intra-articular corticosteroids on articular cartilage-A systemic review". *Orthopaedic Journal of Sports Medicine* 3.5 (2015): 2325967115581163.

8. Dogan N., *et al*. "The effects of ketorolac and morphine on articular cartilage and synovium in the rabbit knee joint". *Canadian Journal of Physiology and Pharmacology* 82.7 (2004): 502-505.

9. Riggin CN., *et al*. "Intra-articular tibiofemoral injection of a nonsteroidal anti-inflammatory drug has no detrimental effects on joint mechanics in a rat model". *Journal of Orthopaedic Research* 32.11 (2014): 1512-1519.

10. Schroeder S., *et al*. "Local tolerance of intraarticular administration of lornoxicam into the rabbit knee joint". *Rheumatology International* 32.9 (2012): 2661-2667.

11. Beitzel K., *et al*. "The effect of ketorolac tromethamine, methylprednisolone, and platelet-rich plasma on human chondrocyte and tenocyte viability". *Arthroscopy* 29.7 (2013): 1164-1174.

12. Su HK., et al. "Pharmacokinetics and four-week repeated-dose toxicity of hyaluronic acid and ketorolac combination following intra-articular administration in

13. Park CW., *et al*. "Comparison of piroxicam pharmacokinetics and anti-inflammatory effect in rats after intra-articular and intramuscular administration". *Biomolecules and Therapeutics* 22.3 (2014): 260-266.

14. Jean YH., *et al*. "Intra-articular injection of the cyclooxygenase-2 inhibitor parecoxib attenuates osteoarthritis progression in anterior cruciate ligament-transected knee inrats: role of excitatory amino acids". *OsteoArthritis and Cartilage* 15.6 (2007): 638-645.

15. Park CW., *et al*. "Four-week toxicity and toxicokinetics of piroxicam and hyaluronic acid combination following intra-articular injection in normal rats". *Molecular and Cellular Toxicology* 10.3 (2014): 319-328.

16. Kim HS., *et al*. "Determination of piroxicam from rat articular tissue and plasma based on LC-MS/MS". *Archives of Pharmacal Research* 39.12 (2016): 1653-1662.

17. Reuben SS and Cornelly NR. "Postoperative Analgesia for Outpatient Arthroscopic Knee Surgery with Intraarticular Bupivacaine and Ketorolac". *Anesthesia and Analgesia* 80.6 (1995): 1154-1157.

18. Convery PN., *et al*. "Low-dose intra-articular ketorolac for pain relief following arthroscopy of the knee joint". *Anaesthesia* 53.11 (1998): 1125-1129.

19. Gupta., *et al*. "Postoperative pain following knee arthroscopy: the effects of intra-articular ketorolac and/or morphine". *Regional Anesthesia and Pain Medicine* 24.3 (1999): 225-230.

20. Calmet., *et al*. "Analgesic effect of intra-articular ketorolac in knee arthroscopy: comparison of morphine and bupivacaine". *Knee Surgery, Sports Traumatology, Arthroscopy* 12.6 (2004): 552-555.

21. Vintar N., *et al*. "Intra-articular patient-controlled regional anaesthesia after arthroscopically assisted anterior cruciate ligament reconstruction:ropivacaine/morphine/ketorolac versus ropivacaine/morphine". *Anesthesia and Analgesia* 101.2 (2005): 573-578.

22. Ng HP., *et al*. "Efficacy of Intra-articular Bupivacaine, Ropivacaine, or a Combination of Ropivacaine, Morphine, and Ketorolac on Postoperative Pain Relief after Ambulatory Arthroscopic Knee Surgery: A Randomized Double-Blind Study". *Journal of Advanced Research* 31.1 (2006): 26-33.

23. Faranak R., *et al*. "Comparison of the effects of intra-articular sole ropivacaine and combined ketorolac and ropivacaine for pain control after knee arthroscopy surgery". *British Journal of Pain* 9.3 (2015): 149-156.

24. Stalman A., *et al*. "Ketorolac but not morphine exerts inflammatory and metabolic effects in synovial membrane after knee arthroscopy: a double blind randomized prospective study using the microdialysis technique". *Regional Anesthesia and Pain Medicine* 34.6 (2009):557-64.

25. Proffen BL., *et al*. "The Effect of Perioperative Ketorolac on the Clinical Failure Rate of Meniscal Repair". *The Orthopaedic Journal of Sports Medicine* 2.5 (2014):1-9.

26. Chaumeron A., *et al*. "Periarticular injection in knee arthroplasty improves quadriceps function". *Clinical Orthopaedics and Related Research* 471.7 (2013): 2284-2295.

27. Perret M., *et al*. "Comparison of patient outcomes in periarticular and intraarticular local anaesthetic infiltration techniques in total knee arthroplasty". *Journal of Orthopaedic Surgery and Research* 10 (2015): 119.

28. Spangehl., *et al*. "The Chitranjan Ranawat Award: Periarticular injections and femoral & sciatic blocks provide similar pain relief after TKA: a randomized clinical trial". *Clinical Orthopaedics and Related Research* 473.1 (2015): 45-53.

29. LEE SC., *et al*. "Rapid analgesic onset of intra-articular hyaluronic acid with ketorolac in osteoarthritis of the knee". *Journal of Back and Musculoskeletal Rehabilitation* 24.1 (2011): 31-38.

30. Euppayo., *et al*. "Effect of hyaluronic acid combined with anti-inflammatory drugs compared with hyaluronic acid alone, in clinical trials and experiments in osteoarthritis: a systemic review and meta-analysis". *BMC Musculoskeletal Disorders* 18.1 (2017): 387.

31. Yoon KH and Nava IMK. "Efficacy and safety of intra-articular ketorolac in the treatment of inflammatory arthritis – A report of the initial experience with 40 patients". *Annals of the Academy of Medicine* 44 (2015): 417-422.

32. Axelsson., *et al*. "Intraarticular administration of ketorolac, morphine, and ropivacaine combined with intraarticular patient-controlled analgesia for pain relief after shoulder surgery: a randomized, double-blind study". *Anesthesia and Analgesia* 106.1 (2008): 328-333.

33. Kim II S., *et al*. "A comparative study on the analgesic effect of continuous intraarticular infusion with ropivacaine, ropivacaine/fentanyl, and ropivacaine/fentanyl/ketorolac after arthroscopic shoulder surgery". *Korean Journal of Anesthesiology* 56.3 (2009): 303-308.

34. Min KS., *et al*. "A double-blind randomized controlled trial comparing the effects of subacromial injection with corticosteroid versus NSAID in patients with shoulder impingement syndrome". *Journal of Shoulder and Elbow Surgery* 22.5. (2013): 595-601.

35. Akhtar., *et al*. "Comparison of intra articular NSAID (ketorolac) injection versus hyaluronic acid injection for the mean decrease of pain score (according to UCLA shoulder rating scale) in the management of adhesive capsulitis". *Pakistan Journal of Pharmaceutical Sciences* 32.3 (2019): 953-956.

36. Xu J., *et al*. "Effect of ketorolac in intra-articular injection analgesia for postoperative pain in patients undergoing shoulder arthroscopy: a pilot-controlled clinical study". *Journal of Pain Research* 12 (2019): 417-422.

37. Park., *et al*. "Ultrasound guided intra-articular ketorolac versus corticosteroid injection in osteoarthritis of the hip: a retrospective comparative study". *Skeletal Radio* 44.9 (2015): 1333-1340.

38. Koh SH., *et al*. "Ultrasound-guided intra-articular injection of hyaluronic acid and ketorolac for osteoarthritis of the carpometacarpal joint of the thumb". *Medicine* 98.19 (2019): 1-7.

39. Olkkola KT., *et al*. "Pharmacokinetics of Oxicam Nonsteroidal Anti-Inflammatory Agents". *Clinical Pharmacokinetics* 26.2 (1994): 107-120.

40. Izdes S., *et al*. "The effects of preoperative inflammation on the analgesic efficacy of intraarticular piroxicam for outpatient knee arthroscopy: 8AP5". *Anesthesia and Analgesia* 97.4 (2003): 1016-1019.

41. Rais K., *et al*. "Intrarticular piroxicam for postoperative analgesia after knee arthroscopic surgery". *European Journal of Anaesthesiology* 25 (2008): 117.

42. Yoon KH and Nava IML. "Intraarticular Piroxicam as a novel therapeutic approach for the treatment of inflammatory arthritis: An initial report of 60 patients". Singapore Society of Rheumatology-Malaysia Society of Rheumatology Combined Meeting. Poster Presentation (2015).

43. Talu GK., *et al*. "Comparison of efficacy of intraarticular application of tenoxicam, bupivacaine nd tenoxicam: bupivacaine combination in arthroscopic knee surgery". *Knee Surgery, Sports Traumatology, Arthroscopy* 10.6 (2002): 355-360.

44. Amin S., *et al*. "The effect of the addition of lornoxicam (xefocam) intraarticular on the WOMAC Scale in patients undergoing arthroscopic anterior cruciate ligament reconstruction". *Middle East Journal of Anesthesiology* 21.1 (2011): 15-21.

45. Balabanova RM., *et al*. "Dynamic changes in synovitis activity after intra-articular administration of xefocam in patients with rheumatoid arthritis (according to clinical and device examinations)". *Ter Arkh* 75.5 (2003): 33-35.

46. Cheer SM. "Parecoxib (parecoxib sodium)". *Drugs* 61.8 (2001): 1133-1141.

47. Parina., *et al*. "Comparison of the Effects of Parecoxib and Diclofenac in Preemptive Analgesia: A Prospective, Randomized, Assessor-Blind, Single-Dose, Parallel-Group Study in Patients Undergoing Elective General Surgery". *Current Therapeutics Research* 65.5 (2004): 383-393.

48. Lloyd R., *et al*. "Intravenous or intramuscular pareocoxib for acute postoperative pain in adults (Review)". *Cochrane Database of Systemic Reviews* 2 (2009): 1-39.

49. Siribumrungwong K., *et al*. "Comparing parecoxib and ketorolac as preemptive analgesia in patients undergoing posterior lumbar spinal fusion: a prospective randomized double-blinded placebo-controlled trial". *BMC Musculoskeletal Disorders* 16 (2015): 59.

50. Du X and Gu J. "The efficacy and safety of pareocoxib for reducing pain and opioid consumption following total knee arthroplasty: A meta-analysis of randomized controlled trials". *International Journal of Surgery* 59 (2018): 67-74.

51. Peng HM., *et al*. "Preemptive Analgesia with Parecoxib in Total Hip Arthroplasty: A Randomized, Double-Blind, Placebo-Controlled Trial". *Pain Physician* 21.5 (2018): 483-488.

52. Moonla R., *et al*. "Comparison of Preoperative and Postoperative Parecoxib Administration for Pain Control Following Major Spine Surgery". *Asian Spine Journal* 12.5 (2018): 893-901.

53. Bian YY., *et al*. "Role of Parecoxib Sodium in the Multimodal Analgesia after Total Knee Arthroplasty: A Randomized Double-blinded Controlled Trial". *Orthopaedic Surgery* 10.4 (2018): 321-327.

54. Essex MN., *et al*. "A randomized study of the efficacy and safety of parecoxib for the treatment of pain following total knee arthroplasty in Korean patients". *Journal of Pain Research* 11 (2018): 427-433.

55. Schug SA., *et al.* "The safety profile of parecoxib for the treatment of postoperative pain: a pooled analysis of 28 randomized, double-blind, placebo-controlled clinical trials and a review of over 10 years of postauthorization data". *Journal of Pain Research* 10 (2017): 2451-2459.

56. Yoon KH and Nava IMK. "Efficacy and safety of intra-articular injection of the cyclooxygenase-2(COX-2) inhibitor Pareocoxib in the treatment of inflammatory arthritis- a report of the initial experience with 60 Asian patients". Australian Rheumatology Associations 57th ASM Poster Presentation (2016).

57. Yoon KH and Nava IMK. "Intra-articular Pareocoxib injection for the treatment of inflammatory arthritis following total knee arthroplasty-A report of 8 Asian patients". Australian Rheumatology Associations 57th ASM Poster Presentation (2016).

58. Lu L., *et al*. "Clinical efficacy of intra-articular pareocoxib injection for the treatment of early knee osteoarthritis". *Zhongguo Gu Shang* 32.5 (2019): 418-422.

59. Yoon KH and Nava IMK. "Therapeutic success of ultrasound-guided injection of hip osteoarthritis with hyaluronic acid-Report of a single centre experience with 18 patients". Singapore- Malaysia Rheumatology Society Workshop (2015). Poster presentation.

60. Mazzocca AD., *et al*. "An in vitro evaluation of the anti-inflammatory effects of platelet-rich plasma, ketorolac, and methylprednisolone". *Arthroscopy* 29.4 (2013): 675-683.

61. Murakami AM., *et al*. "MRI evaluation of rotational alignment and synovitis in patients with pain after total knee replacement". *Journal of Bone and Joint Surgery* 94.9 (2012): 1209-1215.

62. Tanavalee A., *et al*. "Inflammation related to synovectomy during total knee replacement in patients with primary osteoarthritis". *Journal of Bone and Joint Surgery* 93.8 (2011): 1065-1070.

Volume 10 Issue 11 November 2019