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Review Article

Intra-Articular Injections for Pain Relief Following Knee Arthroscopy: A Literature Review

Mohammad Ayati Firoozabadi[1], Behzad Nezhad Tabrizi[2], Seyed Mohammad Milad Seyed Tabaei[2], Alireza Moharrami[2], Seyed Mohammad Javad Mortazavi[3,*]

[1] Assistant Professor, Department of Orthopedic Surgery, Joint Reconstruction Research Center, Imam Khomeini Hospital Complex, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[2] Resident, Department of Orthopedic Surgery, Joint Reconstruction Research Center, Imam Khomeini Hospital Complex, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[3] Professor, Department of Orthopedic Surgery, Joint Reconstruction Research Center, Imam Khomeini Hospital Complex, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[*]Corresponding author: Seyed Mohammad Javad Mortazavi; Department of Orthopedic Surgery, Joint Reconstruction Research Center, Imam Khomeini Hospital Complex, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran. Tel: +98-2166581586, Email: smjmort@yahoo.com

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Abstract

Arthroscopy procedures for the knee are excellent and tend to be outpatient procedures. Pain control after arthroscopic surgery is an important aspect of patient satisfaction and quicker return to daily activities following surgery. The objective of this article was to review the current literature regarding pain management after knee arthroscopy using intra-articular (IA) injections. Our goal in this article is to review the drugs that have been suggested in various articles for IA injections following knee arthroscopy to control pain. In conclusion, the current evidence suggests that combining IA lidocaine and morphine with tranexamic acid (TXA), in addition to ketorolac, is effective for pain relief after arthroscopic knee surgery.

Keywords: Knee; Arthroscopy; Pain; Intra-Articular Injections

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Background

One of the most common orthopedic surgeries is knee arthroscopy. In both arthroscopic and open knee surgeries, the results of knee arthroscopy are better than open knee surgery; therefore, this is one of the reasons why this type of surgery is growing in popularity. Recent advances in the anterior cruciate ligament (ACL) reconstruction techniques, anesthesia, and rehabilitation have made it possible for patients to return to daily activities sooner after surgery (1).

It is well known that outpatient arthroscopic surgery is popular among physicians and patients, but in any case, pain control is an important topic, and with better pain control after arthroscopic knee surgery, patients' satisfaction will increase, and they can return to their daily lives immediately. After ACL reconstruction surgery, various analgesics are usually prescribed, but they may not be sufficient to provide adequate pain relief. Therefore, other analgesic methods such as regional analgesia (femoral nerve block, adductor canal block), local instillation analgesia, and intra-articular (IA) injection are also used (1-6).

Our objective was to review the current literature regarding IA injections following knee arthroscopy. In this article, we summarize all the drugs used to control pain after arthroscopic surgery and provide a description of the pharmacological structure of each drug along with its related studies.

Medications

Bupivacaine: The amino-amide anesthetic drug bupivacaine is like lidocaine; it is also an amino-amide anesthetic drug. An amide bond connects the aromatic head and the hydrocarbon chain rather than an ester bond as in previous local anesthetics. Therefore, amino-amide anesthetics are more stable and less likely to cause allergic reactions. They have the molecular formula of $C_{18}H_{28}N_2O$. Figure 1.A shows the two-dimensional chemical structure of bupivacaine.

In vitro, a study by Piper et al. shows that local anesthetics such as bupivacaine, lidocaine, and ropivacaine are chondrotoxic to human articular cartilage. Longer exposure to higher concentrations of local anesthetics is associated with a greater risk of chondrolysis. Local anesthetics should be used with caution in joints with compromised cartilage, including continuous infusions of bupivacaine and lidocaine at high concentrations (7). An IA injection of bupivacaine significantly reduced the visual analog scale (VAS) score compared to an IA injection of saline (2). Morphine, bupivacaine, and epinephrine, as well as bupivacaine and epinephrine combined with IA injection of epinephrine, led to significantly lower pain symptoms and the use of narcotics compared with epinephrine alone (8). Mitra et al. found that IA injections of bupivacaine-fentanyl relieved postoperative pain in knee arthroscopy patients most effectively, and they also had no side effects (9).

In another study, IA bupivacaine was effective in controlling pain after knee arthroscopy, with no short-term side effects. Low-dose IA bupivacaine 0.5% should be combined with epinephrine adjuvant (10). A study by Yang et al. found that single-dose IA bupivacaine combined with morphine effectively treated pain after knee arthroscopy (11). Based on the available literature, single-dose IA bupivacaine is significantly more effective than a placebo for relieving pain after knee arthroscopy. A randomized controlled trial (RCT) is needed to evaluate long-term side effects, even though no short-term side effects have been reported (12).

Morphine: Morphine is one of the natural alkaloids found in the opium plant. Its molecular formula is $C_{17}H_{19}NO_3$. Figure 1.B shows the two-dimensional chemical structure of morphine.

A study by Dogan et al. examined the effects of ketorolac and morphine on articular cartilage and synovium in rabbit knee joints. Results showed that morphine did not cause severe histopathological changes on the tenth day, and the degree of histopathological changes had regressed by then. A study showed that IA morphine caused transient histopathological changes during an early period, but no contraindications were found for its use as a postoperative analgesic agent (13). During arthroscopic knee surgery, single-dose IA morphine was administered, so that supplementary analgesics could be avoided and the interval before the next procedure could be extended (14). A study by Secrist et al. randomized patients to receive normal saline, tenoxicam, or morphine. Postoperative pain was measured using the VAS, and analgesic requirements were measured. A higher dose of IA morphine provided a better analgesic effect. The pain scores were similar between the tenoxicam and morphine groups 30 minutes postoperatively, but the analgesic requirements with tenoxicam were significantly lower than those with morphine 3-6 hours postoperatively. As compared to IA saline, IA morphine alone, and IA bupivacaine, an IA bupivacaine-morphine injection significantly reduced VAS scores and analgesic consumption (2).

In a study published in the Annals of Surgery, Brandsson et al. looked at the effects of IA or intravenous (IV) morphine and saline on postoperative pain. The pain score was significantly lower in the IA morphine group than in the IV and control groups throughout the entire postoperative period, but there was no significant difference in the need for additional analgesics between the four groups either during the first two postoperative days or during the first postoperative week (15).

In a study by Gupta et al., morphine and ketorolac injected intraocularly resulted in excellent analgesia up to 48 hours following the operation (16). According to the study, morphine, bupivacaine, and epinephrine, as well as bupivacaine and epinephrine, when used in knee arthroscopy, resulted in lower pain scores and decreased narcotic consumption in the recovery room, which are statistically significant when compared with epinephrine alone (8). In arthroscopic knee surgery, bupivacaine plus morphine significantly relieved postoperative pain without increasing short-term side effects compared to bupivacaine alone (11). The VAS scores for pain intensity were not different for 1 mg IA morphine and placebo at early, medium, or late phases (17).

Tramadol: As a synthetic analgesic with central effects, tramadol is a serotonin/norepinephrine reuptake inhibitor (SNRI) and is structurally related to codeine and morphine. For the treatment of moderate to severe pain, tramadol is generally considered a low-risk drug. Its molecular formula is $C_{16}H_{25}NO_2$. The two-dimensional chemical structure of tramadol is shown in figure 1.C and D.

Based on an evaluation and comparison of the analgesic efficacy of IA bupivacaine alone, bupivacaine plus fentanyl, and bupivacaine plus tramadol for postoperative pain relief in Mitra et al.'s study, the mean VAS pain scores were lowest for bupivacaine plus fentanyl, intermediate for bupivacaine plus tramadol, and highest for bupivacaine (9).

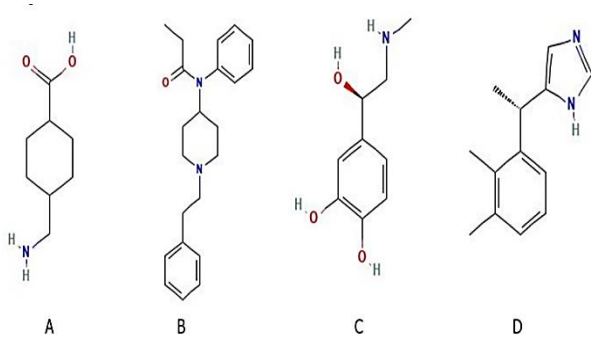

Figure 1. A. The two-dimensional chemical structure of bupivacaine; B. The two-dimensional chemical structure of morphine; C and D. The two-dimensional chemical structure of tramadol

Ropivacaine: The amide-type local anesthetic (Amide Caine) is ropivacaine, a piperidine carboxamide-based compound. Its molecular formula is $C_{17}H_{26}N_2O$. The two-dimensional chemical structure of ropivacaine is shown in figure 2.A.

According to Zhou et al., administering single-dose ropivacaine at the end of arthroscopic knee surgery provided superior pain relief during the first eight postoperative hours without increasing short-term side effects, and rescue analgesia requirements did not differ between the ropivacaine and control groups. Although statistically significant differences were observed in the immediate and early postoperative periods (18).

Ketorolac: Ketorolac is a racemate comprising equimolar amounts of (R)-(+)- and (S)-(-)-5-benzoyl-2,3 dihydro-1H-pyrrolizine-1-carboxylic acid. While only the (S)-(-) enantiomer is a cyclooxygenase-1 (COX1) and COX2 inhibitor, the (R)-(+) enantiomer exhibits potent analgesic activity. Its molecular formula is $C_{15}H_{13}NO_3$. The two-dimensional chemical structure of ketorolac is shown in figure 2.B.

The results of Dogan et al.'s study show that ketorolac does not cause significant histopathological changes and the degree of histopathological changes regresses after ten days (13). The effects of IA administration of ketorolac in the knee joints of rats were investigated by Irwin et al. Thirty rats received ketorolac trometamol injections into the right knee and injections into the left knee as controls. The knees of patients treated with ketorolac had significantly more inflammation at all examination times (19). Merkely et al. reviewed the available evidence on possible deleterious effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on chondrocytes and included 18 studies: 4 in vitro studies, 13 animal studies, and 1 human study. As evidenced by these studies, NSAIDs do not harm healthy mature chondrocytes; however, they may inhibit chondrocyte differentiation and graft incorporation following transplantation of chondrocytes or osteochondral grafts. They recommend that NSAIDs, whether local or systemic, not be used after cartilage repair procedures unless the patient would otherwise be denied a substantial clinical benefit (20).

Xu et al. conducted a retrospective study in which patients with unilateral knee osteoarthritis (OA) receiving five weekly injections were enrolled. There was no difference in pain relief and functional improvement between IA ketorolac injections and corticosteroid injections. Corticosteroids were injected three times a week into group A, followed by 0.5% lidocaine injections twice a week (21).

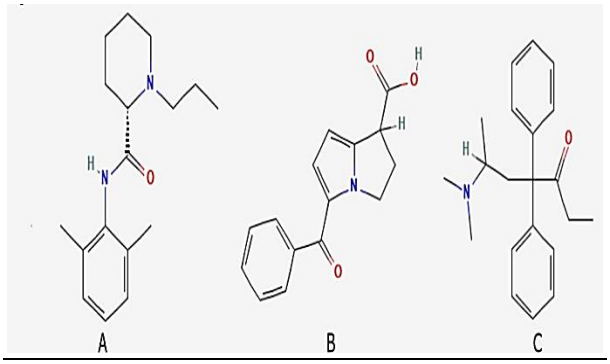

Figure 2. A. The two-dimensional chemical structure of ropivacaine; B. The two-dimensional chemical structure of ketorolac; C. The two-dimensional chemical structure of methadone

A meta-analysis included ten RCTs involving 402 patients, according to Wan et al. The impact of ketorolac supplementation on pain scores after knee arthroscopy was favorable; a longer time between the first analgesic need and fewer analgesics were required, and there was no significant effect on analgesic consumption (22). Xu et al. conducted a pilot-controlled clinical study on 60 patients and showed that adding ketorolac to IA injection of analgesia improved pain relief after shoulder arthroscopy (23).

A study by Xu et al. showed that IV injection of morphine and ketorolac provided excellent analgesia for 48 hours after surgery. Ketorolac also provided significantly better analgesia than either placebo or morphine alone and even better than ketorolac injected intra-articularly (23). According to Brill and Plaza's review study, IA administration of clonidine and ketorolac after arthroscopic knee surgery may reduce postoperative pain (24).

Methadone: Methadone is a synthetic opioid that has analgesic properties. Unlike morphine and morphine-like drugs, methadone acts primarily on the mu-receptor. Its molecular formula is $C_{21}H_{27}NO$. The two-dimensional chemical structure of methadone is shown in figure 2.C.

The Stewart et al. study involved 65 subjects, 25 of whom were in the methadone group, 21 in the morphine group, and 19 in the control group. During the entire postoperative period, no significant differences in supplemental analgesic requirements or pain scores were observed between the methadone and the control groups (25). In a systematic review by Secrist et al., there were no significant differences between IA methadone and IA saline (2).

Tenoxicam: Tenoxicam has anti-inflammatory, analgesic, and antipyretic properties. It functions as an NSAID. Besides being a heteroaryl hydroxy compound, it is a monocarboxylic acid amide, a member of the pyridine family, and a thienothiazine.

Its molecular formula is $C_{13}H_{11}N_3O_4S_2$. The two-dimensional chemical structure of tenoxicam is shown in figure 3.A.

Ozyuvaci et al. studied the possible local adverse effects of IA administration of tenoxicam in rat knee joints. As a control, 50 rats were injected with 0.25 ml of 0.9% saline solution and 0.25 ml of tenoxicam when the right knee joint was injected. These findings suggest that caution should be exercised when injecting IA tenoxicam for post-operative analgesia. No pathological changes were observed in the 7-day, 14-day, or 21-day specimens, as well as in the control joints (26). A study by Secrist et al. demonstrated that IA tenoxicam provided better analgesia than the control group (2).

Sufentanil: Sufentanil is an opioid analgesic that is an anilid resulting from the formal condensation of the aryl amino group of 4-(methoxymethyl)-N-phenyl-1-[2-(2-thienyl) ethyl] piperidin-4-amine with propanoic acid. Its molecular formula is $C_{22}H_{30}N_2O_2S$. The two-dimensional chemical structure of sufentanil is shown in figure 3.B.

Armellin et al.'s randomized, blinded study was designed to measure the effectiveness of IA sufentanil, ropivacaine, and clonidine compared to ropivacaine and clonidine without sufentanil on postoperative pain after arthroscopic reconstruction of the ACL of the knee. This study showed that the addition of sufentanil to the IA solution did not improve pain control (27).

The study by Wang et al. examines the effects of combined local anesthetic and opioid analgesia after single-bundle ACL reconstruction. This study compared the effect of local anesthetic (ropivacaine), opioid (sufentanil), and the combination of these two (ropivacaine combined with sufentanil). The pain scores of the three experimental groups were significantly lower than the controls in every aspect. Both at 6 and 24 hours after the operation, ropivacaine with sufentanil resulted in a lower pain score than ropivacaine or group D (sufentanil). Following the reconstruction of the ACL, injection of an opioid (sufentanil), a local anesthetic (ropivacaine), or a combination of the two can reduce pain significantly (28). Kizilkaya et al. studied the effects of IA saline, sufentanil, and sufentanil and methylprednisolone after knee arthroscopic meniscectomy. Postoperatively, all operations were performed under general anesthesia. Analgesic consumption was significantly reduced in the groups receiving IA sufentanil and sufentanil plus methylprednisolone. Significant differences were also observed between the control and the other two groups. No side effects were observed following the administration of IA sufentanil and sufentanil plus methylprednisolone. Postoperative infections were not observed in any patient (29).

In Vranken et al. study, IA sufentanil was assessed for its effectiveness in preventing postoperative pain after day-case arthroscopic surgery. Pain scores were significantly lower in the two IA sufentanil groups postoperatively and the day after surgery. The control group consumed significantly more additional analgesics. Sufentanil IA administration after outpatient diagnostic arthroscopic knee procedures is a simple, effective, safe, and well-tolerated technique that offers superior postoperative pain control to IV sufentanil (30).

Clonidine: Clonidine is a derivative of imidazoline that acts as a central alpha-adrenergic agonist with antihypertensive properties. Clonidine stimulates alpha-2 adrenergic receptors and reduces the release of norepinephrine (NE), thereby reducing sympathetic outflow to the heart, kidneys, and peripheral arteries. Decreases in sympathetic output lead to decreased peripheral vascular resistance, decreased blood pressure, and decreased heart rate. Furthermore, clonidine binds to the imidazoline receptor subgroup 1 (I1), which may also lower blood pressure. Its molecular formula is $C_9H_9Cl_2N_3$. The two-dimensional chemical structure of clonidine is shown in figure 3.C.

The Brill and Plaza study reviewed seven articles on the use of clonidine. All the articles comparing clonidine to morphine found their analgesic effects to be similar and unrelated to vascular uptake (24), except for Johns et al.'s study, which found clonidine to be superior (31).

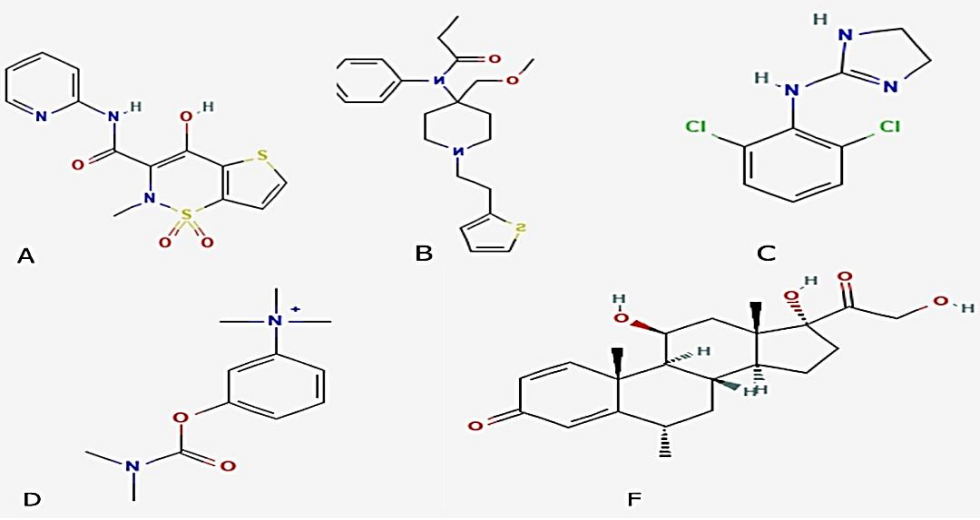

Figure 3. A. The two-dimensional chemical structure of tenoxicam; B. The two-dimensional chemical structure of sufentanil; C. The two-dimensional chemical structure of clonidine; D. The two-dimensional chemical structure of neostigmine; F. The two-dimensional chemical structure of methylprednisolone

In this review, we suggest that clonidine may reduce postoperative pain due to the synergistic effect of both drugs. Based on Sun et al.'s systematic review, clonidine reduced pain intensity for the first 4 hours after surgery, the incidence of postoperative nausea, and the use of rescue analgesics, but increased the risk of hypotension. After surgery, VAS scores were used to measure pain intensity at 1, 2, 4, 6, 12, and 24 hours, and the results of the combined analysis showed significant differences between clonidine and placebo on the VAS scores at 1, 2, 4, and 24 hours after surgery (32).

Neostigmine: Neostigmine is an acetylcholinesterase inhibitor acting as a parasympathomimetic. Its molecular formula is $C_{12}H_{19}N_2O_2^+$. The two-dimensional chemical structure of neostigmine is shown in figure 3.D.

Brill and Plaza examined RCTs of IA clonidine, neostigmine, steroids, and NSAIDs following arthroscopic knee surgery (24). Yang et al. examined the analgesic effects of peripheral muscarinic receptors by administering IA neostigmine after knee arthroscopy in two articles. An arthroscopic meniscus repair was performed under general anesthesia in sixty patients randomized to receive IA neostigmine or IA morphine, and the control group received IA saline microgram neostigmine, and it was revealed that IA administration of the acetylcholinesterase inhibitor neostigmine produced a moderate but significant analgesic effect (11). Brill and Plaza evaluated the effects of IA clonidine and neostigmine on postoperative analgesia in knee arthroscopy patients and found that either IA clonidine or IA neostigmine alone produced postoperative analgesia without being more effective than both (24).

Methylprednisolone: Metaprednisolone is a synthetic corticosteroid that inhibits inflammation and modulates the immune system. Methylprednisolone binds to specific nuclear receptors and activates them, which alters gene expression and inhibits the production of proinflammatory cytokines.

Its molecular formula is $C_{22}H_{30}O_5$. The two-dimensional chemical structure of methylprednisolone is shown in figure 3.F.

Xu et al. studied patients with unilateral symptomatic knee OA receiving 5 weekly injections in a retrospective manner. Results demonstrate that IA ketorolac and corticosteroid injections produce the same pain relief and functional improvement. Group A received 3 weekly injections of corticosteroids, followed by 2 weekly injections of 0.5% lidocaine (21).

Tranexamic Acid (TXA): TXA is a synthetic derivative of the amino acid lysine that has antifibrinolytic properties. TXA, which binds strongly to the five lysine-binding sites of plasminogen, inhibits the conversion of plasminogen into plasmin, thus preventing fibrinolysis. Its molecular formula is $C_8H_{15}NO_2$. The two-dimensional chemical structure of TXA is shown in figure 4.A.

In the study by Chiang et al., 304 patients who underwent arthroscopic ACL reconstruction with autologous hamstring grafts showed that IA injection of TXA after ACL reconstruction significantly reduced postoperative bleeding on day one. In the early postoperative period, both hemarthrosis grade and pain decreased significantly (33). In Johns et al. systematic review, four prospective RCTs administered IV TXA in bolus or infusion form before ACL reconstruction, while two studies administered IA injections of TXA. An aggregate of 533 ACL reconstruction procedures from four trials examined postoperative hemarthrosis grade after TXA administration. As a result of IV TXA administration during ACL reconstruction surgery, there was a significant reduction in joint drain output and hemarthrosis as well as improvement in pain scores and range of motion in the early postoperative period without increased complications. At 2 weeks, the TXA-treated cohort had a significantly lower mean postoperative hemarthrosis grade (31). In this prospective and randomized study, 120 patients who underwent arthroscopic ACL reconstruction were included. Results of the study show that both IV and IA injections can reduce IA hemarthrosis, joint pain, and swelling following ACL reconstruction. There are no significant differences between IV and IA injections regarding the efficacy of reducing hemarthrosis, joint pain, and swelling. The administration of IV TXA can reduce the amount of drainage blood and postoperative hemarthrosis after ACL reconstruction without causing side effects (34).

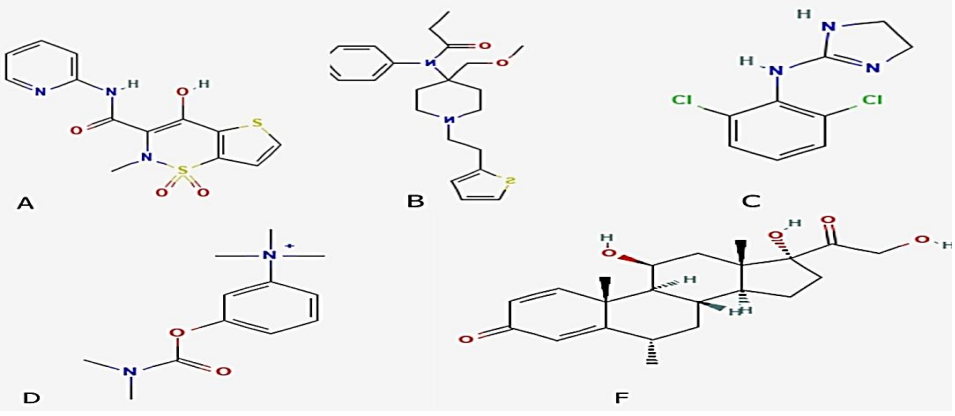

Figure 4. A. The two-dimensional chemical structure of tranexamic acid (TXA); B. The two-dimensional chemical structure of fentanyl; C. The two-dimensional chemical structure of epinephrine; D and F. The two-dimensional chemical structure of dexmedetomidine

Davey et al.'s study evaluated the use of TXA to reduce postoperative hemarthrosis and pain after ACL reconstruction in three RCTs. The results of two RCTs indicate a significant difference between TXA administered intraoperatively and no TXA administered intraoperatively in VAS scores three days later. There is promising evidence for using some oral and IV administration of TXA to reduce postoperative opioid use (35).

Fentanyl: A lipophilic phenylpiperidine opioid agonist, fentanyl has analgesic and anesthetic properties. A mechanism of action is mediated by the selective binding and activation of the mu-receptor in the central nervous system (CNS), which mimics the effects of endogenous opiates. Guanosine triphosphate (GTP) is exchanged for guanosine diphosphate (GDP) on the G-protein complex after mu-subtype opioid receptors are activated, inhibiting adenylate cyclase. The result is a decrease in intracellular cyclic adenosine monophosphate (cAMP), which inhibits cAMP-mediated calcium influx through the calcium channels, resulting in hyperpolarization and reduced neuron excitability. Its molecular formula is $C_{22}H_{28}N_2O$. The two-dimensional chemical structure of fentanyl is shown in figure 4.B.

Lu et al. meta-analysis assessed the safety and efficacy of IA fentanyl supplementation in four RCTs. Fentanyl IA supplementation is associated with decreased pain scores in 1-hour controlled studies (36). A study by Mitra et al. found that IA injection of bupivacaine and fentanyl relieved postoperative pain effectively in patients undergoing knee arthroscopy, and there were no adverse effects (9).

Epinephrine: The hormone epinephrine, also known as adrenaline, is secreted by the adrenal glands and has diverse functions that make it a potential drug. Its molecular formula is $C_9H_{13}NO_3$. The two-dimensional chemical structure of epinephrine is shown in figure 4.C.

A prospective study suggests that morphine, bupivacaine, and epinephrine injections, as well as bupivacaine and epinephrine injections used in knee arthroscopy, resulted in lower pain scores and decreased narcotic consumption in the recovery room when compared with epinephrine alone (18).

Dexmedetomidine: Dexmedetomidine is an imidazole derivative and active d-isomer of medetomidine with analgesic, anxiolytic, and sedative properties. The dexmedetomidine inhibits the release of NE from synaptic vesicles by selectively binding to presynaptic alpha-2 adrenoceptors. Its molecular formula is $C_{13}H_{16}N_2$. The two-dimensional chemical structure of dexmedetomidine is shown in figure 4.D and F.

The Peng et al. systematic review identified RCTs comparing IA dexmedetomidine with control for postoperative analgesia in knee arthroscopy. It significantly decreased postoperative pain and opioid consumption in patients undergoing arthroscopic knee surgery. In addition, a longer time before the first request for postoperative analgesia was also indicated by dexmedetomidine (37).

Magnesium: Magnesium cation acts as an osmotic laxative and calculi-dissolving agent. There is a magnesium ion exchange activity and a magnesium osmotic activity in the magnesium cation. There are two types of magnesium cations: magnesium (2+) is a divalent metal cation and a monoatomic dication. It has a role as a cofactor and a geroprotector. Its molecular formula is Mg^{2+}.

Shi et al. compared the postoperative pain outcomes after knee arthroscopy with versus without IA Mg in a meta-analysis of RCTs. There were significantly fewer pain scores at rest and with movement 2, 4, 12, and 24 hours after surgery, lower doses of supplemental opioid consumption, and a longer time to the first analgesic requirement in the IA Mg group than in the control group. There was no significant difference between the groups in terms of adverse reactions (38).

Conclusion

As a result of our initial database search using our search strategy, 15 review articles and 18 articles were identified about IA anesthesia. In conclusion, the current evidence suggests that combining IA lidocaine and morphine with TXA, in addition to ketorolac, is effective for pain relief after arthroscopic knee surgery.

Conflict of Interest

The authors declare no conflict of interest in this study.

Acknowledgements

None.

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