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Research Progress on the Application of "Cocktail" Therapy in Total Knee Arthroplasty

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Abstract: ***Total knee arthroplasty is one of the important surgical methods for end-stage knee osteoarthritis in elderly patients. However, due to the large surgical trauma, postoperative pain may occur to varying degrees, which not only affects patients' functional exercise, delays limb rehabilitation and increases hospitalization time but also increases postoperative medical expenses and complications risks. In recent years, the widely used joint periarticular local infiltration "cocktail" has become an ideal combination therapy for multimodal analgesia. This method aims to prevent and control postoperative pain by co-injecting several drugs (formulated drugs) into the surrounding area of the joint. Currently, the "cocktail" formulation is constantly being improved, and there is still a lack of unified standards regarding its formulation, injection method, and site. This article will review recent research progress on the use of "cocktail" treatment in total knee arthroplasty both domestically and internationally.***

Keywords: Knee osteoarthritis, Total knee arthroplasty, Cocktail therapy, Pain, Local injection**.**

1. Introduction

Knee osteoarthritis (KOA) is one of the most common chronic degenerative joint diseases, characterized by degeneration and loss of articular cartilage, irreversible structural changes in the joint margins and subchondral bone formation [1-2]. Its onset may be related to factors such as chronic overuse, obesity, trauma-induced joint instability, and genetics [3]. Early-stage knee osteoarthritis can be improved through conservative treatments such as modifying physical activity and lifestyle habits, physical therapy, and oral anti-inflammatory analgesics. Total knee arthroplasty (TKA) is one of the important measures used when non-surgical treatments are ineffective or conservative methods have poor outcomes, especially for elderly patients with end-stage knee osteoarthritis. The TKA procedure involves bone resection and soft tissue release, which can cause persistent postoperative pain [4-5]. The continuous severe pain after surgery not only significantly affects early patient recovery but also prolongs hospitalization time and increases economic burden. It also leads to increased consumption of opioid drugs and contradicts the concept of fast-track rehabilitation [6-7], thereby affecting patient satisfaction. Currently, there are many methods used for pain control after TKA surgery; however, they all have certain limitations. Mainstream pain control methods include epidural anesthesia outside the spinal range, patient-controlled analgesia (PCA), peripheral nerve blockade such as femoral nerve blockade (FNB), adductor canal blockade (ACB), and local infiltration analgesia (LIA) [6]. Oral, intramuscular, or intravenous administration of opioid analgesics may lead to complications such as respiratory depression, sedation, nausea, vomiting, renal dysfunction and smooth muscle inhibition; peripheral nerve blockade and epidural catheter analgesia are complex procedures with high technical requirements that carry risks of nerve damage, hematoma formation and infection. Additionally, femoral nerve block (FNB) can result in decreased quadriceps strength and increased risk of falls during hospitalization. In comparison, local infiltration anesthesia (LIA), also known as the "cocktail" technique, has been widely recognized as an ideal combination for multimodal pain management. This method involves direct injection of a small amount of medication into the site of pain during surgery to eliminate pain at its source with fewer postoperative adverse reactions. It was first proposed and applied by Bianconi et al. [8] in TKA surgery. The "cocktail" technique is simpler to perform compared to other analgesic methods, reduces the use of opioid analgesics without increasing the risk of infection. Currently there is still a lack of standardized guidelines regarding the formulation, injection method and site selection for the "cocktail", which remains controversial for certain drugs and injection sites.

2. Cocktail Recipe

Currently, there is no consensus on the formula for the "cocktail" therapy, and a unified standard has not been established. The preparation of the "cocktail" medication involves mixing multiple formulas, with local anesthetics being primarily used as its main ingredient and can be combined with non-steroidal anti-inflammatory drugs, adrenaline, opioid drugs, and glucocorticoids.

3. Mechanism of Action of Cocktail Drugs

3.1 Local Anesthetic Drugs

Local anesthetics exert analgesic effects by increasing the nerve impulse threshold, inhibiting depolarization rate of electrical potential, and prolonging the refractory period of action potential [9]. Amide derivatives such as ropivacaine, bupivacaine, and levobupivacaine are commonly used in "cocktails" for local anesthesia [10], all of which belong to long-acting local anesthetics. Among them, ropivacaine has advantages including vasoconstriction, low toxicity to the heart and central nervous system, early achievement of sensory-motor blockade at low concentrations, and greater patient tolerance. Compared to bupivacaine, ropivacaine exhibits lower efficacy on neural tissue function, lipid solubility, and toxic reactions; furthermore, it demonstrates a more pronounced sensory blockade than motor blockade and surpasses bupivacaine in terms of degree of separation

between sensory and motor blockades [11]. It is precisely these characteristics that make ropivacaine the most commonly used local anesthetic in clinical practice.

3.2 Modification of Non-steroidal Anti-inflammatory Drugs

As an important component of the "cocktail" formula, nonsteroidal anti-inflammatory drugs (NSAIDs) have significant effects on pain caused by tissue damage and inflammation. They mainly reduce the release of inflammatory mediators by inhibiting the synthesis of prostaglandins (PGs) in peripheral tissues, thereby suppressing vasodilation and tissue edema to alleviate inflammatory reactions. At the same time, they can also decrease the sensitivity of peripheral receptors to pain-inducing substances such as bradykinin and block the transmission of pain signals. Currently, ketorolac is the most commonly used NSAID. Kg [12] et al., in their study, found that local injection of a "cocktail" containing ketorolac during surgery significantly alleviated severe pain experienced during early walking. M [13] et al., compared with placebo or oral celecoxib, discovered that periarticular injection of a multimodal analgesic containing ketorolac could significantly relieve postoperative pain and improve range of motion (ROM). Gramk [14] et al., through their research, indicated that including NSAIDs in a periarticular "cocktail" may help reduce surgical-induced inflammatory responses and ultimately alleviate postoperative pain conditions.

3.3 Epinephrine

Epinephrine is a vasoconstrictor that works by activating vascular smooth muscles on α receptors, causing blood vessel constriction. This prolongs the absorption time of local anesthetics and provides assistance in maintaining the intensity and duration of other drugs in the "cocktail". Additionally, using epinephrine in multimodal analgesic cocktails for periarticular injections can lead to reduced local blood flow, thereby decreasing local anesthetic toxicity [15]. Research by Salwan et al. [16] also suggests that combining bupivacaine with epinephrine helps constrict blood vessels at the injection site, ultimately keeping bupivacaine localized and extending its effect duration. Furthermore, it can cause contraction of small arterial smooth muscle fibers and potentially minimize intra-articular bleeding. A randomized double-blind trial [17] showed lower visual analog scale (VAS) scores and nursing pain assessment after adding α2-adrenergic agonists to periarticular infiltration injections during surgery's early postoperative period. However, due to its vasoconstrictive properties, subcutaneous application of epinephrine should be avoided to prevent skin ischemic necrosis and poor wound healing; caution should also be exercised when using it in patients with hypertension, organic heart disease, or coronary artery disease based on its effects on the cardiovascular system. Nevertheless, no literature reports were found by the authors indicating a significant increase in complications or adverse reactions following total knee arthroplasty (TKA) when adding epinephrine to periarticular injection "cocktails", which requires further experimental verification.

3.4 Opioid Drugs

As a central analgesic, opioid drugs can produce analgesic effects through central analgesic mechanisms and also have analgesic effects in peripheral inflammatory tissues. Currently, most research on the addition of opioids to "cocktails" mainly focuses on morphine. Local injection can slow down the absorption of morphine, prolong its duration of action, and reduce the central side effects caused by systemic administration [18]. The half-life of most anesthetics is less than 4 hours, and using only morphine for analgesia has limited duration in postoperative pain management. Some studies have shown that morphine only significantly exerts its effect within 24 hours after total knee arthroplasty (TKA), while persistent pain after knee joint surgery lasts for a long time. Therefore, combination therapy is usually adopted, including opioids, long-acting local anesthetics, and adrenaline to increase sedation effect and prolong their duration. However, there is still controversy over the effectiveness and duration of analgesia when adding morphine alone in local infiltration anesthesia (LIA). Studies by Iwakiri [19] et al. demonstrated that adding morphine to cocktails did not alleviate pain or reduce swelling or improve range of motion (ROM) after surgery. Wang [20] et al., on the other hand, pointed out that adding morphine to analgesic cocktails did not relieve early postoperative pain or restore quadriceps muscle strength or extend daily walking distance but could reduce postoperative consumption of morphine.

3.5 Glucocorticoids

As an important component and key element in the "cocktail", glucocorticoids inhibit pro-inflammatory cytokines, induce anti-inflammatory cytokines, reduce prostaglandin synthesis, thereby decreasing the excitability of local pain receptors [20-22]. These drugs have powerful anti-inflammatory and analgesic effects, can reduce surgical stress reactions, alleviate swelling and pain while prolonging the duration of local analgesia [23-24]. Currently, treatment mainly involves using combination betamethasone injection solution, dexamethasone injection solution, and injectable methylprednisolone as medium to long-acting glucocorticoids. Among them, combination betamethasone injection solution is increasingly favored by clinicians. This medication contains soluble betamethasone sodium phosphate and slightly soluble betamethasone dipropionate. Soluble betamethasone sodium phosphate is rapidly absorbed and effective, while slightly soluble betamethasone dipropionate acts as a slow-release storage agent with prolonged efficacy for achieving long-term symptom relief [25]. Luo et al. [25] studied 50 patients who received ropivacaine treatment alone and 50 patients who received ropivacaine, betamethasone, and morphine knee joint injections. The results showed that the VAS scores in the betamethasone group were lower than those in the control group, and it enhanced early functional recovery of the knee joint. Revised sentence: Zheng et al. [21] found that patients who received local application of betamethasone after total knee arthroplasty (TKA) had significantly improved maximum extension angle, maximum flexion angle, and passive range of motion on the third day after surgery compared to the control group. Kulkarni et al. [26] demonstrated in their study that adding methylprednisolone injection to a cocktail can significantly alleviate early postoperative pain in TKA patients and promote faster recovery of knee flexion function. These

studies all demonstrate the powerful anti-inflammatory and analgesic effects of glucocorticoids. However, there is still controversy regarding the effectiveness and safety of glucocorticoids, as some studies suggest they may increase the risk of adverse reactions such as postoperative infections. The authors believe that the occurrence rate is dose- and time-dependent, and typically low-dose local application cocktails containing glucocorticoids are used; however, more validation is needed in the future to assess postoperative adverse reactions and complications.

3.6 Other Drugs

3.6.1 sulfate of magnesium (MgSO4)

Recent studies have added MgSO4 as an adjuvant analgesic to multimodal analgesic cocktails. MgSO4 is an effective postoperative adjunct medication [27] with anti-inflammatory properties. Its analgesic ability is related to its antagonistic action on N-methyl-D-aspartate (NMDA) receptors in the peripheral and central nervous systems or modulation of calcium influx into cells [28-29]. NMDA receptors play a crucial role in transmitting and regulating acute nociceptive hypersensitivity associated with central pain transmission [30]. As an NMDA receptor antagonist, MgSO4 can reduce the demand for anesthesia and analgesics after surgery. Zhao et al.'s study demonstrated that adding MgSO4 to a multimodal analgesic cocktail can prolong postoperative pain relief, decrease opioid consumption, and effectively alleviate early postoperative pain conditions following total knee arthroplasty (TKA), without accelerating functional recovery [31]. Wang et al.'s meta-analysis showed that MgSO4 significantly enhanced the analgesic efficacy of the cocktail during the early stage after TKA surgery [32]. Additionally, adding MgSO4 appeared to reduce opioid consumption without increasing adverse reaction rates. However, one study reported no significant analgesic advantage when adding MgSO4 to the cocktail among TKA patients [33]. These findings need further confirmation in future research.

3.6.2 Aminocaproic acid

With the rise of accelerated surgical rehabilitation concepts, postoperative pain and bleeding issues have received increasing attention. Increased blood loss in patients can lead to an increase in transfusion rates and may cause transfusion-related complications, thereby affecting limb recovery. Therefore, reducing perioperative blood loss is particularly crucial in total knee arthroplasty (TKA). Among the multimodal analgesic drugs, adding hemostatic agents has become one of the important means to control post-TKA bleeding. Tranexamic acid is commonly used as a hemostatic agent in cocktail therapy. It belongs to the category of antifibrinolytic drugs and achieves hemostasis by blocking the binding of plasminogen with fibrinogen and inhibiting fibrinolysis caused by plasminogen activators, while also blocking activated inflammatory reactions to alleviate postoperative pain. However, due to its inhibitory effect on fibrinolysis, tranexamic acid may theoretically increase the risk of venous thromboembolism while reducing perioperative blood loss in TKA. Therefore, caution should be exercised when using tranexamic acid to prevent adverse events such as deep vein thrombosis from occurring. Singh et al.'s study [34] demonstrated that treatment regimens containing tranexamic acid effectively controlled postoperative pain and significantly reduced blood loss, thereby decreasing transfusion requirements and hospital stay duration.

4. The Injection Method and Site of the Cocktail

Currently, there is very little research on the effect of injection methods and sites on pain relief, and there is a lack of unified standards. The choice of injection site relies more on the personal preference of the operator. Currently used injection methods mainly include periarticular injections (anterior injections, posterior injections) and intra-articular irrigation [35]. The anterior injections mainly cover areas such as the medial and lateral collateral ligaments, infrapatellar fat pad, patellar ligament, quadriceps femoris muscle, and suprapatellar pouch. The posterior injections mainly refer to the posterior joint capsule. Pain caused by tension in the muscles and tendons around the knee joint during flexion-extension activities after surgery is concentrated primarily around the quadriceps tendon extensor mechanism and medial collateral ligament due to limited release of these structures during surgery. Li et al. [36] conducted a study comparing 25 patients who received preoperative intra-articular injections with 25 patients who received postoperative intra-articular injections for treatment purposes. They demonstrated that using a mixture of analgesic substances injected into the anterior aspect of the joint can significantly alleviate early postoperative pain following total knee arthroplasty (TKA) while improving knee joint function with high safety levels. There is some controversy regarding intra-articular injection of the posterior joint capsule of the knee. Supporters of injecting a cocktail into the posterior joint capsule argue that the local anesthetic included in it has a permeating effect, and during postoperative bed rest, the local anesthetic can disperse to the posterior region, blocking nerves that supply the posterior aspect of the knee joint and further relieving pain. Mortazavi et al. [35] demonstrated through their study that peripheral injections were associated with less early postoperative pain and greater active flexion of the knee joint when combined with intra-articular (IA) and periarticular (PA) methods compared to using only one method. Nakai et al. [37] found in their research that multimodal drug periarticular injections after total knee arthroplasty (TKA) significantly reduced analgesic requirements without significant risks. However, some scholars [38] believe there is no need for injection into the posterior joint capsule as these areas are not substantially damaged during surgery. There are risks involved in injecting drugs into this area due to structures such as popliteal artery, popliteal vein, tibial nerve and common peroneal nerve located in close proximity to it; furthermore, drug entry into blood vessels may lead to cardiac arrhythmias.

Recently, researchers have applied the "cocktail" technique to subperiosteal injection. The periosteum can be divided into two layers, with the outer layer being a dense fibrous membrane that covers the surface of the periosteum, effectively preventing leakage of the "cocktail". The inner surface is rich in non-neural fibers and small blood vessels, which are sensitive to local anesthetics and can significantly

reduce pain. Therefore, it is feasible to use the "cocktail" for subperiosteal injection in practice. Wang et al. [39] divided patients into a local infiltration group and a subperiosteal injection group, and compared to the local infiltration group, subperiosteal injection with the "cocktail" therapy could significantly alleviate pain and reduce bleeding.

5. Combining "cocktail" of Multi-modal Pain Relief Methods

In recent years, there has been rapid development in analgesic medications and techniques, leading to the widespread application of multimodal analgesia in the field of surgery. Perioperative multimodal analgesia can effectively alleviate postoperative pain and increase the motivation for active functional exercise in patients undergoing total knee arthroplasty (TKA), thereby improving patient satisfaction. With the deepening promotion of the concept of fast-track surgery, the use of multimodal analgesia in TKA has also been greatly advanced. Multimodal analgesia reduces pain by acting on multiple receptor sites along peripheral and central nociceptive pathways, thereby reducing inflammatory reactions and sensitivity to intense stimuli. With the continuous development of ultrasound imaging combined with anesthesia techniques, visualized nerve block techniques have been applied to TKA to relieve postoperative pain. The perioperative period for TKA often adopts a combination "cocktail" approach for multimodal analgesia, including femoral nerve block and adductor canal block. Wang et al.'s [40] study demonstrated that combining femoral nerve block with local knee joint injection can effectively prolong postoperative pain relief time after total knee arthroplasty with fewer side effects while providing satisfactory postoperative analgesic effect. Yuenyongviwat et al. [41] found that combined adductor canal block was more effective than using adductor canal block alone in reducing postoperative pain and fentanyl consumption in patients undergoing total knee arthroplasty (TKA). Luo et al. [42] demonstrated that adductor canal block combined with local injection of multimodal analgesics provided better early pain control, reduced the need for opioid drugs, improved sleep quality, and did not increase the incidence of complications. These studies suggest that the combination of "cocktail" nerve blocks is becoming increasingly popular among clinicians as a multimodal analgesic approach, and its analgesic effect is superior to single analgesic methods.

6. The Restrictiveness of Cocktails

There is a lack of unified standards for the drug formulation, injection method, and site in the 'cocktail' therapy. There is still controversy over the selection of specific drugs and their injection sites. For example, combining adrenaline, glucocorticoids, and local anesthetics in the formulated drugs can enhance analgesic effects and prolong pain relief time; however, further research is needed to prove their safety and effectiveness clinically. In addition, the "cocktail" cannot provide long-lasting analgesic effects, so there has been no decrease in demand for opioid analgesics. However, with the development of new long-acting local anesthetics, novel nonsteroidal anti-inflammatory drugs (NSAIDs), and more extensive research being conducted, these issues may gradually be resolved.

7. Summary

The "cocktail" therapy is a relatively novel postoperative analgesic method for total knee arthroplasty (TKA), which has been widely recognized and extensively used in TKA surgeries due to its simplicity. With the advancement of preemptive analgesia and multimodal analgesic techniques, combining preoperative peripheral nerve blockade with periarticular local infiltration analgesia can provide excellent and long-lasting pain relief without increasing the risk of adverse reactions or complications, promoting patient recovery speed, and improving patient satisfaction. In summary, the 'cocktail' therapy is characterized by its simplicity, overall safety, and effectiveness, making it worth promoting in TKA surgeries; however, further research is needed on drug formulation, injection methods, and site selection.

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