

Current Status and Progress of Perioperative LIA in Elderly Patients with Femoral Neck Fractures during THA

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Abstract: Elderly patients with femoral neck fractures face major challenges in postoperative pain due to their special clinical characteristics. Such patients often suffer from multiple complications and have poor tolerance to traditional analgesia options. Pain is one of the most important factors affecting postoperative rehabilitation. Therefore, effective measures should be taken to manage perioperative pain during the perioperative period. It is important to manage perioperative pain. The introduction of the concept of Enhanced Recovery After Surgery (ERAS) provides new ideas to solve this problem. The existing evidence shows that the "fast track management" model based on RERAS concept can significantly shorten the hospitalization time of elderly fracture patients and reduce the incidence of postoperative complications and death within the year. In the multimodal analgesia of ERAS concept, "Cocktail" local infiltration analgesia (LIA) analgesia is an important part. This article summarizes the current research status and controversy of cocktail therapy under the concept of rapid rehabilitation.

Keywords: ERSAS; Pain; Advanced Age; Femoral Neck Fracture; LIA.

1. LIA's Core Position in the RERAS Concept

In the ERAS concept, LIA multi-modal analgesia plays a key role. Compared with traditional single analgesic regimens, this combination medication strategy can significantly reduce opioid dosage and improve postoperative recovery treatment [2]. Studies have confirmed that in patients undergoing full arthroplasty, the addition of LIA-based multimodal analgesic regimen can reduce the median daily oral morphine equivalent consumption from 52 to 22, while significantly improving pain scores [3]. The advantage of LIA is that it can not only fully analgesic through the synergistic effect of different drugs, but also minimize the adverse reactions of a single drug, which is crucial for older patients [3]. [1]

2. Introduction to "LIA"

LIA is an important part of perioperative multimodal analgesia during joint replacement [4]. In clinical practice, one or more drugs with analgesic effects are injected into multiple points around the joint capsule, and the local anesthesia or anti-inflammatory and analgesic effects of the drug are used to reduce wound pain. This method is called LIA [5,6]. This technology was originally proposed by M. Bianconi [7]. After a long period of development, LIA is currently mainly composed of local anesthetics, epinephrine, glucocorticoids, morphine, non-steroidal anti-inflammatory drugs and other drugs. In addition, drugs such as tranexamic acid will be added to increase the hemostatic effect. Therefore, LIA can simultaneously exert various effects such as analgesia [8], hemostasis [9], swelling and anti-inflammatory

[10].

2.1. Subject-Local anesthetic

The analgesic time of LIA mainly depends on the action time of local anesthetics. Local anesthetics exert analgesic effects by increasing the electrical threshold of nerve impulses, inhibiting the depolarization rate, and prolonging the refractory period. Peripheral injections can be performed individually or in combination with other drugs. Currently, local anesthetics commonly used in LIA include ropivacaine and bupivacaine. However, compared with bupivacaine, ropivacaine has the characteristics of sensorimotor isolation. It does not reduce postoperative muscle strength while achieving effective analgesia, and the patient is better tolerated [11]. At the same time, due to its lower neurotoxicity and cardiotoxicity [12], it is therefore safer. Therefore, it has obvious advantages in postoperative analgesia of THA. Clinical studies have shown that 0.5% ropivacaine 20ml for PENG block can significantly improve the postoperative analgesic effect [13], while 0.2% ropivacaine 20ml for obturator nerve block also showed good opioid-saving effects [14]. It is worth noting that 0.33% ropivacaine 30ml for post-quadruple muscle block can significantly reduce the dosage of morphine after hip arthroplasty [15]. Although bupivacaine is more analgesic, it should be used with caution in elderly patients due to its potential cardiotoxicity [16].

2.2. Commonly used adjuvants

2.2.1. Adrenaline

Adrenaline is often used for peri-articular injections and serves as an important adjuvant in LIA. It is a sympathomimetic catecholamine that affects alpha and beta

adrenergic receptors, where its effect on alpha-1 receptor increases vascular smooth muscle contraction. Therefore, through this mechanism, Brigid Brown et al. [17, 18] proposed that combined ropivacaine and adrenaline constitute LIA. The study found that it not only provides a good analgesic effect, but also does not increase the compensation dosage of postoperative analgesics. The reason is that the effect of epinephrine contracting blood vessels, on the one hand, it can reduce bleeding in the surgical area [19], and on the other hand, it can slow down drug absorption, thereby prolonging the time of action of the drug [20]. In addition, local combined use of epinephrine [21] will not increase the incidence of complications such as skin necrosis or skin laceration.

2.2.2. Glucocorticoids

Glucocorticoids exert a powerful anti-inflammatory effect by inhibiting the inflammatory cascade, while reducing capillary permeability and reducing inflammatory factors' exudation, thereby reducing stimulation in the surgical area and reducing pain in the surgical oral. In THA multimodal analgesia, dexamethasone as an auxiliary drug showed good analgesic enhancement effects [22]. The study found that a local anesthetic mixture containing 2 mg of dexamethasone was used for anterior lumbar quadruplegia block, which can significantly improve pain control in patients with daytime hip arthroscopy [23]. However, the potential impact of glucocorticoids on wound healing still needs to be vigilant [24]. Glucocorticoids will accelerate the progress of osteoporosis [25], increase blood sugar [26], and promote the progress of cardiovascular disease in the elderly [27], etc.

2.2.3. Non-steroidal Anti-inflammatory Drugs

In clinical practice, nonsteroidal anti-inflammatory drugs are often used as important adjuvants for LIA. It blocks the synthesis of arachidonic acid prostaglandin (PG) by inhibiting cyclooxygenase (COX), thereby inhibiting the inflammatory response caused by PG and relieving pain. Combined with ropivacaine, it can reduce the production and release of inflammatory factors, inhibit inflammatory response, prolong the action time of local anesthetics, reduce local tissue edema, and promote incision healing [11,28]. In post-THA analgesia, nonselective NSAIDs, although the analgesic effect is comparable to COX-2 inhibitors, the former may lead to more adverse reactions [29]. The combination of acetaminophen and celecoxib has been shown to improve recovery quality and reduce opioid demand [30]. However, NSAIDs have similar effects in pain relief and functional improvement compared with glucocorticoids, but the incidence of total adverse events in the NSAIDs group is higher [29].

2.2.4. Morphine

Clinically, it was found that after the application of routine LIA, some patients still experience obvious pain. Especially for elderly patients, due to poor tolerance to pain, they still need to use drugs such as morphine or tramadol for remedial analgesia after the operation. Therefore, whether it is possible to enhance the analgesic effect of LIA by directly adding drugs such as morphine [31], so that patients can get out of bed as soon as possible, and speed up rapid postoperative recovery has become the research direction. Morphine can bind to the central and surrounding opioid receptors, inhibit the pain area of the cerebral cortex and produce a strong analgesic effect. It is also necessary to consider that although the addition of morphine can enhance the analgesic effect, due to the special pharmacological effects of morphine, it is easy

to produce various adverse reactions such as addiction, nausea and vomiting, excessive sedation, and respiratory depression [11]. Therefore, the indications and drug dosage of morphine need to be strictly grasped.

2.2.5. Tranexamic Acid

Bleeding is also another challenge that THA needs to face. Studies have shown [9,32] that bleeding is one of the important factors affecting rapid recovery after joint replacement surgery, so effective hemostasis measures should be taken during the perioperative period. Tranexamic acid is a competitive inhibitor of plasminogen, which is an integral part of the fibrinolytic pathway necessary for hemostasis [33], and has good prospects for the treatment of surgical bleeding during orthopedic surgery. Generally speaking, tranexamic acid is administered intravenously, but recent studies have confirmed that tranexamic acid can also be used locally, such as intraarticular medication, local infiltration around the joint, etc. [34]. Moreover, the study found that compared with intravenous injection of tranexamic acid, blood loss was significantly reduced after local tranexamic acid surgery. At the same time, local infiltration of tranexamic acid [35,36] can also reduce the risk of perioperative adverse reactions, such as nausea, intraoperative hypotension and blood transfusion, and will not increase the risk of venous thrombosis [37].

3. Comparison of Clinical Evidence on Drug Combination Regimens

3.1. A Summary of Randomized Controlled Trials of Dual Regimens (Local Anesthetics +NSAIDs)

Several randomized controlled trials have confirmed that the dual combination of local anesthesia and NSAIDs is the basic solution for post-total hip arthroplasty. The RECIPE trial compared the dual combination of acetaminophen and ibuprofen, and the results showed that this regimen was effective in controlling postoperative pain and reducing opioid demand [13]. Another study combined PENG block (ropivacaine) with celecoxib and acetaminophen, significantly improved the quality of patients' recovery and reduced opioid dosage [14]. Network meta-analysis showed that in patients undergoing THA under spinal anesthesia, local anesthetic infiltration combined with COX-2 inhibitors reduced the resting VAS score by 1.6 points and 2.3 points during activity [38, 39]. It is worth noting that the effect of the dual regimen is dose-dependent, and the analgesic effect of ibuprofen 400mgq6h is significantly better than that of the low dose regimen [40].

3.2. Strengthening Evidence for the Analgesic Effect of Triple Regimen (With Glucocorticoid)

In the triple regimen, the addition of glucocorticoids showed a clear analgesic enhancement effect. RECIPE trials have confirmed that adding dexamethasone on the basis of local anesthetics and NSAIDs can reduce the morphine dose by 7.5 mg 24 hours after surgery, and at the same time extend the first analgesic time by 2.8 hours [13,40]. Systematic reviews show that a triple regimen containing dexamethasone can reduce the pain score of THA patients by an additional 1.2 points (95%CI-1.6 to -0.8) 48 hours after surgery [41]. In some studies, the triple regimen of dexamethasone added

significantly improved the analgesic effect of 6 and 12 hours after surgery [23]. However, it should be noted that the dose effect curve of glucocorticoids shows a platform phenomenon in the range of 4-8 mg, and higher doses do not bring additional benefits [41].

3.3. Marginal Benefits and Increasing Risks of Four or More Schemes

In the four-linked and above regimens (local anesthetics + NSAIDs + glucocorticoids + adjuvant drugs), network meta-analysis showed that although the addition of adrenaline and opioids on a dual-linked basis can reduce the VAS score by an additional 0.5 points after 6 hours of surgery, the incidence of nausea and vomiting increased by 18% [38,39]. Although the quadruple combination of PENG block combined with local infiltration anesthesia (LIA) reduced the early pain score, there was no significant difference in the analgesic effect after 24 hours compared with the triple protocol [23]. It is worth noting that when more than four drug combinations, each additional drug brings only 0.2 points of VAS improvement, while the risk of adverse reactions increases linearly [42]. Among the elderly patients, there was no statistically different functional recovery indicators compared with the triple scheme, but the incidence of cognitive dysfunction was significantly increased [14].

4. Long-term Prognosis and Patient Satisfaction

Long-term prognostic evaluation includes joint function scores and patient satisfaction for 3-12 months. Cohort study data showed that Oxford hip score (OHS) 3 months after surgery predicted long-term functional recovery in 12-24 months [43]. It is worth noting that although multimodal analgesia can reduce opioid-related adverse reactions in the short term [16], its improvement in long-term patient satisfaction still requires more high-quality evidence to support [44]. Existing studies have shown that the satisfaction score of patients with three-drug combination regimens (local anesthetics + NSAIDs + glucocorticoids) is significantly higher than that of the dual-drug regimen [15], but the marginal benefits of the four-linked and above regimens have not yet shown statistical differences [45].

5. Evidence of Clinical Efficacy

5.1. Analgesic Effect Evaluation Indicators (Pain Score, Morphine Consumption)

LIA optimizes perioperative analgesia through multimodal analgesia. Studies have found that LIA can obtain lower pain scores after surgery [46]. At the same time, the pain scores of 1 and 3 hours after surgery were significantly lower in the patient group combined with PENG block technology (median 2 vs 5) [47]. Opioid consumption is an important objective indicator reflecting the analgesic effect. Studies have shown that optimizing analgesic regimen can reduce the 24-hour oral morphine equivalent dose to 10 mg (15-30 mg in the control group) [47], and every 10-year-old age can reduce the need for opioids by 23% [48].

5.2. Functional Recovery Assessment (Harris Score, Time to Get Out of Bed)

Functional restoration assessment focuses on joint mobility and early exit from bed activity time. The QoR-15

questionnaire evaluation showed that the 24-hour postoperative recovery quality score of patients receiving PENG block combined with multimodal analgesia was significantly improved [49,50]. Network meta-analysis showed that the average time to get out of bed in patients using exercise retention block technology was 8-12 hours earlier than that of traditional analgesic regimens [51]. However, the effect of iliopsoas muscle plane block on the improvement of functional recovery indicators has not been confirmed [49].

5.3. Spectrum Analysis of Complications (Infection, Risk of Fall, Cognitive Dysfunction)

Multimodal analgesia can reduce the incidence of postoperative delirium (confirmed by randomized controlled studies of patients with grade 2-3 ASA scores) [52], while reducing adverse reactions such as opioid-related nausea and vomiting. In terms of risk of infection, the glucocorticoid-containing cocktail formula did not show an increase in the rate of infection at the surgical site [40]. The risk of fall is closely related to analgesic plans. LIA can effectively control pain and improve the patient's early mobility [40], thereby indirectly causing gait instability and falling risk due to pain, and maintain better quadriceps muscle strength (evaluated by postoperative strength test). Another multicenter trial proposed that the perioperative use of an "anti-inflammatory cocktail" strategy can significantly reduce the incidence of POD in elderly patients with hip fracture surgery ($p < 0.05$) and no serious side effects were reported [52].

5.4. Comparison of Incidence of Local Tissue Toxic Reactions

Local anesthetics, as the core component of multimodal analgesic LIA, deserves special attention to its local tissue toxicity. Studies have shown that ropivacaine and bupivacaine have good histocompatibility within the clinically recommended dose range, but high concentrations may still cause reversible damage to muscle and nerve tissue [53]. Studies have shown that ropivacaine and bupivacaine have good histocompatibility within the clinically recommended dose range, but high concentrations may still cause reversible damage to muscle and nerve tissue [53]. In clinical practice, the combination of local anesthetics and adrenaline can prolong the action time and reduce systemic absorption through vasoconstriction, but may increase the risk of ischemia, especially in patients with peripheral vascular diseases, which should be used with caution [23].

5.5. Effect of Glucocorticoids on Wound Healing

The addition of glucocorticoids (such as dexamethasone) is controversial in multimodal analgesic regimens. Data from the RECIPE trial showed that the incidence of wound complications in triple regimens containing dexamethasone was 38%, with no statistical difference compared with those without dexamethasone [54]. However, studies have pointed out that high doses of glucocorticoids may delay wound healing by inhibiting fibroblast proliferation and collagen synthesis, especially in patients with diabetes [55]. Current evidence supports that the perioperative application of single small doses (such as dexamethasone 4-8mg) has a good safety balance, which can not only exert anti-inflammatory and

analgesic effects, but also does not significantly increase the risk of poor wound healing [56].

5.6. Drug Interactions and Systemic Side Effects

Synergies of drugs in multimodal analgesic regimens may be accompanied by potential risk of drug interactions. The combination of NSAIDs and antiplatelet drugs may increase the risk of postoperative bleeding, while the addition of opioids may cause typical adverse reactions such as respiratory depression and intestinal obstruction. Denmark's national cohort study showed that 63% of patients with combined use of NSAIDs and opioids after THA surgery experienced at least one drug-related adverse reaction, which was significantly higher than that of the single-agent treatment group [57]. Of particular concern is the elderly patient population, whose liver and renal function may lead to slowing drug metabolism and increase the risk of accumulation toxicity [32] [58]. Clinical monitoring should focus on changes in renal function indicators and neurological symptoms, and timely adjust the drug dose or replace the alternative.

5.7. Benefits of Morphine LIA -Risks

Morphine has a clear effect in postoperative analgesia. Especially in multimodal analgesic regimens, morphine combined with non-steroidal anti-inflammatory drugs and local anesthetics can achieve synergistic analgesia through the "opioid saving strategy" and significantly improve early postoperative activities [41]. Studies have found that morphine-added cocktails can indeed reduce the total opioid dose and improve analgesic effects in THA, but the risk of adverse reactions needs to be weighed (respiratory depression, nausea, vomiting, excessive sedation, etc.). Currently, it is recommended to give priority to non-opioid multimodal analgesia, morphine is only used as an auxiliary or remedial measure, and needs to be used under strict testing [40].

6. Special Considerations for Medication for Elderly Patients

6.1. Special Considerations for Medication for Elderly Patients

Patients with chronic pain (especially secondary to osteoarthritis) need a more intensive analgesic regimen after THA. Studies have shown that the need for opioids in this type of patients is 47% higher than that in ordinary patients at 48 hours after surgery [59]. It is recommended to adopt the "three-stage" solution: The basic medication is 0.5% bupivacaine combined with ketorolac tromethamine (30mg), and dexamethasone (4-8mg) is added in the second step. 0.1mg of clonidine can be added in the third step for patients with refractory pain [15,60]. It is worth noting that patients with chronic pain who have psychological comorbidities (such as depression) have a 38% correlation with psychological status than physiological indicators [61], so psychological intervention is required simultaneously.

6.2. Risk Control for Patients with Comorbidities (Diabetes/Cardiovascular Disease)

For THA patients with diabetes or cardiovascular disease, special attention should be paid to the use of glucocorticoids.

When diabetic patients receive dexamethasone $\geq 8\text{mg}$, the risk of wound infection increases by 2.1 times [62]. It is recommended to adopt a modified formula to avoid glucocorticoids [14,63]. Patients with cardiovascular disease should strictly monitor their adrenaline dosage, and studies have confirmed that the threshold for increased systolic blood pressure is reduced by about 30% in patients with coronary heart disease [64]. For patients with more than two chronic diseases, ultrasound-guided targeted nerve blocks (such as PENG block) are recommended, which can reduce systemic drug use by 60% while maintaining equivalent analgesia [14,65]. Individualized programs for such special populations require multidisciplinary collaboration in anesthesiology, internal medicine and rehabilitation.

6.3. Drug Adjustments in Elderly Patients

Senior patients (≥ 75 years old) face unique challenges in the management of postoperative analgesia of THA, and their drug metabolic capacity has significantly decreased with age. Studies have shown that the risk of serious adverse reactions in patients over 80 years old is 2.3 times higher than that in patients aged 60-69 years old [62]. In drug selection, special attention should be paid to the dose of ropivacaine should be reduced by 30-40%, because its liver metabolic capacity is reduced by about 35% in the elderly [66]. At the same time, elderly patients often have chronic kidney disease, and drugs such as diclofenac with a high proportion of excretion from the kidney should be avoided when using NSAIDs [67]. Latest evidence supports the use of low-dose (0.2% concentration) ropivacaine combined with a 50% reduction in COX-2 inhibitor (such as celecoxib) regimen, which can not only maintain analgesic effects but also significantly reduce the risk of cognitive dysfunction [54,66].

7. Best Practices Supported by Existing Evidence

Current evidence shows that for multimodal analgesic regimens for total hip arthroplasty (THA), based on the dual-unit regimen of local anesthetics (such as 0.2% ropivacaine) combined with NSAIDs, satisfactory analgesic effects can be achieved [14,68]. On this basis, the triple scheme of adding glucocorticoids (such as dexamethasone) can further enhance the analgesic effect and reduce the need for opioids [40,69]. The most recommended scheme is to use a triple cocktail ratio scheme composed of 0.2% ropivacaine + 40 mg methylglucamine + 30 mg ketorolac intraoperatively [69]. The latest research supports the use of regional block techniques (such as PENG block) with local infiltration anesthesia (LIA). This combination regimen can significantly reduce postoperative pain scores, reduce opioid consumption, and retain motor function [70].

8. Conclusion and Outlook

The main limitation of current multimodal analgesic regimens is the lack of precise medication guidance for individual differences in patients, especially for older patients. Emerging research shows that in the future, the difference in patients' responses to specific analgesic drugs may be predicted through preoperative pain sensitivity tests and metabolic gene detection [71], creating conditions for the real implementation of precise analgesics. Secondly, traditional local anesthetics are limited by the problem of short duration of action. Although new drug delivery systems such as

liposome bupivacaine can prolong the action time to 120 hours, their clinical effects are still controversial after 24 hours [72,73], so further research and confirmation is needed. The existing research mainly focuses on the short-term analgesic effect 24-48 hours after surgery, and lacks a systematic assessment of long-term outcomes. In the future, more PCT studies in older people need to be carried out to clarify their impact on long-term prognosis; at the same time, current cocktail therapy is mainly extensive local injection around the joints, which may cause some drug waste. In the future, it is necessary to explore the precision injection technology of "cocktails" under the guidance of supermarkets to improve the analgesic effect on elderly patients.

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