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Research Progress of Intrathecal Morphine in Postoperative Analgesia

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Abstract: Postoperative pain is a common complication in the perioperative period of surgery. It not only reduces patients' quality of life, but also easily induces adverse events such as pulmonary infection and deep vein thrombosis, hindering the clinical implementation of the concept of enhanced recovery after surgery. As a hydrophilic opioid, intrathecal morphine (ITM) has the advantages of long residence time in cerebrospinal fluid and high analgesic potency, which can achieve longterm analgesia for 24–48 hours, especially with a significant effect on visceral pain control. It has become a core component of the multimodal analgesia system. This paper systematically reviews the development status, pharmacological basis and core advantages of ITM in postoperative analgesia, focuses on its clinical application optimization strategies and targeted application schemes in different types of surgery, analyzes the shortcomings of current research, and prospects future research directions, so as to provide accurate and comprehensive practice guidance for clinicians.

Keywords: Intrathecal morphine; Postoperative analgesia; Multimodal analgesia; Enhanced Recovery After Surgery (ERAS)

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1. Introduction

Postoperative pain is a series of physiological, psychological, and behavioral responses experienced by patients following surgical trauma, typically peaking within 24–72 hours post-surgery [1]. Although laparoscopic minimally invasive surgery results in less postoperative pain compared to large-incision open surgery, laparoscopic postoperative pain is predominantly visceral pain, caused by tissue manipulation, visceral dissection, abdominal distension due to pneumoperitoneum, and referred pain. According to statistics, regardless of cancer treatment modalities and tumor locations, 80% of patients report moderate to severe pain [2]. In recent years, scholars both domestically and internationally have achieved numerous breakthroughs in optimizing the clinical application of intrathecal morphine (ITM), developing individualized dosing regimens, and constructing multimodal analgesic strategies. This article systematically reviews the current research status of ITM in postoperative analgesia, providing comprehensive and precise practical references for clinicians, while offering insights for the precise and intelligent development in the field of postoperative analgesia.

2. Development status of intrathecal morphine for postoperative analgesia

Since its first application in 1979, where six patients responded solely to morphine for analgesia with complete pain relief lasting 12–24 hours, ITM has become an integral part of postoperative pain management across multiple surgical disciplines [3]. Currently, the surgical indications for intrathecal morphine are extensive, with recommended doses being < 500 μg for cardiothoracic/abdominal surgeries, 100–200 μg for orthopedic surgeries, 50–200 μg for urological surgeries, < 300 μg for spinal surgeries, and 50–100 μg for cesarean sections. Beyond these advantages, single-dose intrathecal morphine administration is more cost-effective than catheter-based delivery techniques, making it a component of enhanced recovery after surgery protocols [4]. However, significant gaps exist in current research: the quantity and quality of data are low, statistical robustness is weak, and large-sample, multicenter studies targeting specific surgical types are lacking; the synergistic effects of combining intrathecal morphine with non-opioid analgesics remain unclear; and research on the long-term outcomes (e.g., incidence of chronic pain, quality of life) for patients is insufficient [5–7].

3. Pharmacological basis and advantages

3.1. Mechanism of action

ITM exerts analgesic effects by directly acting on μ-opioid receptors in the dorsal horn of the spinal cord, inhibiting the transmission of nociceptive impulses, while also activating descending pain inhibitory pathways in the brainstem to further enhance analgesia [8]. As a hydrophilic opioid, morphine, when administered intrathecally, maintains high concentrations in the cerebrospinal fluid, binding to μ-receptors on the cell membranes of dorsal horn neurons. Through G-protein signaling pathways, it inhibits adenylate cyclase activity, reduces calcium ion influx, and promotes potassium ion efflux, thereby inhibiting the release of nociceptive neurotransmitters (e.g., substance P, glutamate) and blocking the transmission of pain signals to the central nervous system [9].

3.2. Core advantages

3.2.1. Potent and long-lasting analgesia

ITM directly acts on spinal pain transmission pathways, blocking pain signal transmission at its source, resulting in direct and potent analgesic effects. While alleviating early postoperative pain, it reduces opioid consumption and associated adverse reactions, facilitating early patient recovery in line with the principles of enhanced recovery after surgery [10]. Its long-lasting analgesic properties stably cover the peak pain period of 24–48 hours post-surgery, reducing the frequency of postoperative rescue analgesia and avoiding blood concentration fluctuations and analgesic gaps caused by rapid metabolism of short-acting analgesics [11].

3.2.2. Minimal impact on motor function

Unlike local anesthetics, ITM primarily acts on sensory nerve fibers with no significant inhibitory effects on motor nerve conduction [4]. Clinical studies confirm that within the recommended dose range (100–500 μg), intrathecal morphine does not cause motor dysfunction such as lower limb weakness or numbness. ITM provides superior analgesia compared to traditional anesthesia methods in spinal and thoracic surgeres [12].

3.2.3. Reduced systemic adverse reactions

Due to the minimal dosage of ITM and its predominantly local action, the concentration of drugs entering the bloodstream is extremely low, significantly reducing systemic opioid-related adverse reactions. Continuous monitoring is not clinically required for patients receiving ≤ 100 μg of intrathecal morphine [13].

3.2.4. Compatibility with multimodal analgesia concepts

Intrathecal morphine exhibits significant synergistic analgesic effects with local anesthetics, α_2-adrenergic agonists, and NSAIDs. Intrathecal morphine targets and blocks spinal pain transmission, local anesthetics directly inhibit nerve fiber impulse conduction, α_2-adrenergic agonists reduce the release of pain signals, and non-steroidal anti-inflammatory drugs inhibit inflammation-mediated pain sensitization, synergistically amplifying analgesic efficacy through multiple pathways [14].

4. Optimization strategies for clinical application

4.1. Dose refinement and personalization

The intensity, duration, and mechanisms of pain vary significantly across different surgical procedures, necessitating precise adaptation of intrathecal morphine doses based on surgical characteristics to ensure effective analgesia while minimizing safety risks. Although thoracoscopic surgery involves minimally invasive incisions, the sharp pain caused by pleural traction is prominent, peaking within the first 48 hours postoperatively, with a recommended dose of 200 μg [15]. Spinal surgeries such as lumbar fusion, which involve nerve root traction, bone tissue damage, and internal fixation implantation, have a high incidence of severe postoperative pain, warranting doses of 200–300 μg [16]. Pediatric patients, whose physiological functions are not yet fully developed and exhibit unique drug metabolism and cerebrospinal fluid circulation, are recommended a dose of 4–5 μg/kg [17]. Elderly patients, due to degenerative physiological functions and significantly reduced drug metabolism and clearance capabilities, should receive 100–200 μg of intrathecal morphine during hip replacement surgery if they are over 65 years old [13]. Patients with sleep apnea syndrome, who have congenital or acquired abnormalities in respiratory regulation, are more sensitive to the respiratory depressant effects of opioids, requiring a 30–50% reduction in intrathecal morphine dose [18].

4.2. Combination therapy strategies

Multimodal analgesia, centered on "mechanistic complementarity and synergistic enhancement", has become the mainstream approach in the clinical application of intrathecal morphine. By combining analgesic drugs or techniques with different targets and pathways, it not only amplifies the spinal-targeted analgesic effect of intrathecal morphine but also reduces the dose of a single drug, thereby decreasing opioid-related adverse effects [19]. The combination of local anesthetics (e.g., bupivacaine, ropivacaine) with intrathecal morphine allows bupivacaine to immediately block nerve fiber impulse conduction postoperatively, precisely filling the analgesic gap from morphine onset to peak effect, effectively alleviating early postoperative sharp pain, and significantly reducing the required morphine dose and opioid-related adverse effects such as respiratory depression and pruritus [20]. α2-adrenergic agonists (e.g., ketamine, dexmedetomidine) can inhibit neurotransmitter release by activating α2 receptors in the spinal dorsal horn, producing synergistic analgesic effects with morphine. In major abdominal surgeries, the group receiving intrathecal morphine combined with dexmedetomidine demonstrated significantly enhanced analgesia, prolonged time to first rescue analgesia, reduced PCA morphine consumption, and lower pain scores [21]. Nonsteroidal anti-inflammatory drugs (NSAIDs) specifically inhibit cyclooxygenase (COX) activity, reducing prostaglandin synthesis and release in peripheral tissue inflammation, thereby blocking pain signal transmission at its source while inhibiting postoperative pain sensitization. This mechanism precisely complements the central analgesic mechanism of intrathecal morphine, synergistically enhancing overall analgesic efficacy [22].

5. Safety management and adverse effects

Adverse effects of intrathecal morphine are primarily categorized into non-pulmonary complications and respiratory risks [23]. The former commonly manifest as nausea and vomiting, pruritus, and urinary retention; the latter's core risk is respiratory depression, which, although rare, is life-threatening and a key focus of prevention [24].

5.1. Non-pulmonary complications

5.1.1. Nausea and vomiting

Nausea and vomiting are the most common non-pulmonary adverse effects following intrathecal morphine administration. A recent meta-analysis incorporating multiple clinical studies confirmed that the incidence of postoperative nausea and vomiting in patients receiving intrathecal morphine was 1.52 times higher than that in the non-intrathecal morphine control group [24]. A multimodal preventive strategy is clinically employed, involving the combination of at least two prophylactic antiemetics with different mechanisms of action and reducing intraoperative opioid use to synergistically lower the risk of nausea and vomiting [8].

5.1.2. Pruritus

Pruritus is a highly characteristic adverse effect of intrathecal morphine, with an incidence as high as 37–61%, significantly higher than that associated with other postoperative analgesics [25]. Its pathogenesis involves morphine activating γ-aminobutyric acid (GABA)-ergic neurons in the spinal dorsal horn, upregulating the activity of gastrin-releasing peptide receptors. Abnormal activation of these receptors triggers abnormal sensory nerve signal transmission, ultimately causing generalized or localized pruritus [24]. Preoperative prophylactic use of antihistamines, such as 20 mg of diphenhydramine administered orally or intravenously, can mitigate skin pruritus by blocking histamine H1 receptors [26].

5.1.3. Urinary retention

Urinary retention is a common postoperative adverse effect of intrathecal morphine, with an incidence of approximately 6–17.3%. It not only affects patient comfort but may also delay early mobilization and rehabilitation. Its occurrence is closely related to morphine inhibiting spinal micturition reflexes and reducing acetylcholine release, leading to weak bladder detrusor muscle contractions [24].

5.2. Respiratory risks

Respiratory depression is the most severe adverse effect following intrathecal morphine administration. Although its incidence is only 1.1–5.1%, once it occurs, it can rapidly progress to respiratory failure, directly endangering patient life [22]. Continuous vital sign monitoring is strongly recommended within the first 24 hours postoperatively, focusing on three key indicators: respiratory rate, blood oxygen saturation (SpO_2), and level of consciousness [27].

5.3. Other complications

5.3.1. Hypotension

Hypotension is a prominent adverse effect in multimodal intrathecal analgesia, with an incidence as high as 42.37%. Local anesthetics directly block sympathetic nerve conduction, while α2-adrenergic agonists further inhibit sympathetic activity. This dual effect leads to vasodilation and suppressed heart rate regulation, ultimately causing blood pressure to drop [14]. Clinical prevention requires targeted interventions: intraoperative infusion of crystalloid at a dose of 10–15 mL/kg to maintain adequate blood volume; strict avoidance of rapid infusion of vasodilatory drugs to prevent abrupt blood pressure drops.

5.3.2. Puncture-related complications

Puncture-related complications such as epidural hematoma and infection are rare (incidence < 0.1%), primarily associated with improper puncture techniques and inadequate aseptic practices. Intrathecal injections should be performed under sterile conditions using a 27G pencil-point needle to avoid spinal cord injury [28].

6. Application evaluation in different surgical types

Intrathecal morphine (ITM), with its advantages of long-lasting and potent analgesia, has been widely applied in surgeries across multiple fields, including abdominal, thoracic, orthopedic, obstetric and gynecological, and pediatric surgeries. However, its application protocols need to be specifically adjusted according to the pain characteristics of different surgeries and the features of patient populations [12].

6.1. Abdominal surgery

The pain mechanism in abdominal surgery is complex, encompassing sharp incisional pain, visceral distension pain, and peritoneal traction pain. The superimposition of multidimensional pain can delay recovery. The combination of ITM and multimodal analgesia can complement mechanisms and comprehensively meet pain management needs. In laparoscopic colorectal surgery, 150 μg of ITM combined with bupivacaine reduced the postoperative 24-hour Numerical Rating Scale (NRS) score by 2.3 points, decreased opioid consumption by 35%, and did not inhibit gastrointestinal motility [29]. The use of 3 μg/kg of ITM combined with transversus abdominis plane block (TAPB) further reduced opioid consumption, improved pain scores at various time points, accelerated the recovery of gastrointestinal function and activity, and minimized adverse reactions [30]. In open living-donor liver resection, 300 μg of intrathecal morphine combined with bupivacaine significantly reduced postoperative fentanyl consumption and NRS scores for resting, activity, and shoulder pain within 12 hours ($p < 0.001$), demonstrating superior analgesic effects [31]. ITM is widely used in abdominal surgery, alleviating pain, reducing opioid use, and some studies suggest it can shorten hospital stays [32].

6.2. Cardiothoracic surgery

The pain mechanism in thoracic surgery is unique, primarily stemming from chest wall incision trauma, pleural traction caused by surgical manipulation, and intercostal nerve injury. The pain is intense and persistent, severely affecting patient comfort, limiting respiratory amplitude and cough expectoration, and increasing the risk of complications such as pulmonary infection and atelectasis [33]. For cardiac surgery, a recommended dose of 5–10 μg/kg is advised, while for thoracoscopic surgery, a dose of 10 μg/kg provides better analgesic effects. Fixed low doses (e.g., 200 μg) may lead to inadequate analgesia [34,35]. Multiple studies have confirmed that ITM can reduce postoperative 24-hour opioid consumption by 30–50%, with analgesic effects lasting over 48 hours, effectively reducing the need for rescue analgesia [36,37].

6.3. Orthopedic surgery

Pain in orthopedic surgery mainly involves bone, muscle, and nerve injury pain, and there is an urgent need for analgesic protocols that have minimal impact on motor function. In total knee arthroplasty, 100 μg of ITM combined with continuous femoral nerve block reduced the postoperative 24-hour motion pain score by 1.5 points and opioid consumption by 30%, without affecting knee joint mobility [38]. In spinal surgery, ITM can directly act on the spinal cord at the affected segment, providing precise analgesia. In lumbar fusion surgery, 100 μg of ITM reduced patient-controlled analgesia (PCA) morphine consumption and did not affect lumbar mobility, allowing patients to ambulate within 3 days postoperatively [39]. In clinical practice, strict dose control is essential, with individualized adjustments based on different surgical types. Additionally, enhanced postoperative respiratory function monitoring and the combination of multimodal analgesic strategies, such as non-steroidal anti-inflammatory drugs and local blocks, are necessary to balance analgesic effects and safety [40,41].

6.4. Obstetric and gynecological surgery

As a core adjuvant in neuraxial anesthesia for cesarean sections and other obstetric surgeries, ITM offers efficient and long-lasting analgesia. Dose optimization of ITM is crucial for balancing analgesic effects and safety. Multiple guidelines recommend an ITM dose range of 50–100 μg for elective cesarean sections. A domestic randomized controlled study involving 142 parturients confirmed that a 100 μg dose provided ideal postoperative 48-hour analgesia, making it the preferred clinical dose [42,43]. ITM is a safe and effective analgesic method for radical hysterectomy in gynecological malignancies. In radical surgeries, a single dose of ITM (100–200 μg) combined with low-concentration local anesthetics significantly reduced resting and motion pain scores 24–72 hours postoperatively and decreased intravenous opioid use by up to 50% [44,45]. Future research should focus on large-sample studies to determine the optimal dosing protocols for different surgical methods and tumor stages and optimize multimodal analgesic combinations.

6.5. Pediatric surgery

ITM is one of the core methods for multimodal analgesia in pediatric postoperative care. With its advantages of definite analgesia, small drug dosage, and long-lasting effects, it has been widely applied in various pediatric surgeries. The efficacy and safety of a low-dose protocol (2–5 μg/kg) in spinal fusion surgery have been validated, effectively reducing postoperative 24-hour PCA morphine consumption and resulting in significantly lower pain scores compared to the pure PCA group [46]. ITM also shows advantages in pediatric cardiac and abdominal surgeries: a dose of 20 μg/kg provides 12 hours of effective analgesia after sternotomy and has an opioid-sparing effect [47]. Future research should involve multi-center prospective clinical trials to refine dosing protocols for different age groups and surgical types.

6.6. Other surgical types

The analgesic value of ITM has been validated in both high-trauma and minimally invasive urological surgeries. In open prostatectomy and nephrectomy, 250 μg of ITM significantly prolonged the time to the first analgesic requirement [48]. ITM also demonstrates advantages in percutaneous nephrolithotomy and kidney transplantation, reducing not only postoperative pain scores but also the incidence of catheter-related bladder discomfort [49].

7. Future prospects

The future research directions of ITM include conducting multi-center large-sample clinical studies for special populations and complex surgeries to develop standardized dosing guidelines; accelerating the research and development and clinical translation of novel sustained-release formulations to develop long-acting analgesic preparations; exploring the mechanisms of adverse reactions and developing targeted preventive drugs and intervention techniques; and investigating the integration of ITM with artificial intelligence technology, using machine learning algorithms to optimize analgesic protocol development and improve the precision and efficiency of clinical applications.

8. Conclusion

As an important method for postoperative analgesia, ITM exhibits significant analgesic advantages in various fields. Through fine-tuning the dose based on surgical types and individual patient characteristics, precise adaptation of analgesic effects can be achieved, providing high-quality pain management solutions for patients undergoing different surgeries.

Disclosure statement

The authors declare no conflict of interest.

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