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RESEARCH ARTICLE

Optimizing Nefopam Dosing Strategies and Administration Timing while Assessing their Long-Term Influence on Recovery Trajectories and Graft Success

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Introduction

Nefopam is analgesic drug which is a non-opioid, non-nonsteroidal and anti-inflammatory that inhibits the reuptake of serotonin, norepinephrine, and dopamine. It is widely used as an adjuvant for pain. Nefopam has multiple mechanisms therefore it is consider both analgesic and anti-hyperalgesic properties, which is particularly interesting when considering long-term sensitization and recovery. Analgesic drug is Nefopam a centrally acting non-opioid has emerged as a good candidate for inclusion in multimodal analgesia. Nefopam exerts anti-nociceptive effects by inhibiting the synaptosomal reuptake of serotonin, dopamine, and norepinephrine. Nefopam has been reported to be effective in postoperative pain control with an opioid-sparing effect.However, nefopam itself can induce PONV according to some studies and there is relatively little information on the effect of nefopam on PONV when used in combination with fentanyl. Researches revealed that the drug is a centrally acting, non-opioid analgesic and N-methyl-D-aspartate (NMDA) receptor antagonist which inhibits voltage-sensitive sodium channels. Nefopam has been demonstrated as an anti allodynic effects in a neuropathic pain model and the ATP-sensitive potassium channel may be involved. In a rat model study of pain induced by formalin, intrathecal nefopam significantly increased serotonin and norepinephrine levels and it reduced the release of glutamate in the spinal cord. Nausea, vomiting, sweating, dizziness, drowsiness, and tachycardia are known adverse effects of nefopam. Nefopam should be administered with slowly intravenous infusion as a single, 20-mg dose, followed by a continuous infusion of 60 to 120 mg/day. Neuropathic Pain Symptom Inventory (NPSI-T) score is used to assess the Neuropathic pain. This tool utilizes a self-administered questionnaire to evaluate the positive symptoms of neuropathic pain.

Therefore, the aim of this study is to optimize the nefopam dose strategies and administration timing while assessing their long-term influence on recovery trajectories and graft success with other drugs.

Materials and Methods

Study design

A prospective, randomized, controlled study was conducted to evaluate the impact of varying nefopam dosing strategies and administration timing on post-intervention recovery trajectories and graft success. Participants were allocated into three parallel groups: (1) standard-timing nefopam administration, (2) optimized-timing administration, and (3) control analgesic regimen without nefopam. Randomization blocks of six were used to ensure balanced group distribution.

Study population

Eligible participants included individuals scheduled for graft-related procedures (e.g., reconstructive,

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transplant, or tissue-engineered graft placement) who met inclusion criteria:

1. Age ≥ 18 years;
2. Ability to provide informed consent;
3. Absence of contraindications to nefopam;
4. No pre-existing neurological or renal conditions that could confound analgesic pharmacokinetics.

Exclusion criteria included chronic pain requiring long-term analgesics, hypersensitivity to nefopam, hemodynamic instability, or concurrent participation in another investigational drug study.

Intervention: Nefopam dosing and timing strategies

Participants in the nefopam groups received the medication within established clinical safety limits and according to institutional guidelines. Two dosing strategies were tested:

Standard timing group: Nefopam was administered according to the routine peri-operative protocol currently used at the institution.

Optimized timing group: Nefopam was administered based on a pharmacokinetic/-dynamic informed schedule. Optimization criteria included predicted plasma concentration profiles, anticipated intraoperative nociceptive peaks, and individual patient covariates (weight, renal function, expected surgical duration).

All administrations were performed intravenously using identical infusion systems to minimize procedural variability. The control group received the institution's standard non-nefopam analgesic regimen.

Graft procedure standardization

To reduce procedural heterogeneity, all graft procedures were performed by the same surgical team using unified operative protocols. Variables standardized included graft preparation technique, ischemia times (if applicable), intraoperative fluid management, and postoperative immobilization or off-loading strategies.

Outcome measures

Primary outcomes

Recovery trajectory

1. Postoperative pain intensity recorded using a validated pain scale at predefined intervals (0-72 h; 7, 14, and 30 days).
2. Time to first independent ambulation or functional milestone relevant to graft type.
3. Analgesic rescue medication requirements.

Graft success

1. Clinical graft viability assessments (e.g., perfusion, color, edema).
2. Imaging-based evaluation (Doppler, ultrasound, or MRI depending on graft type).
3. Incidence of graft failure within 12-month follow-up.

Secondary outcomes

1. Inflammatory and stress-response biomarkers (e.g., IL-6, CRP, cortisol).
2. Incidence of nefopam-related adverse events.
3. Health-related quality-of-life scores (e.g., EQ-5D).

Data collection and monitoring

All perioperative data were captured using electronic case-report forms. An independent monitoring committee reviewed protocol adherence, adverse events, and data completeness. Pharmacokinetic sampling was conducted in a subset of participants to correlate plasma nefopam levels with analgesic effects and graft outcomes.

Statistical analysis

Sample size calculations were performed based on expected differences in recovery trajectory slope and graft success rates between groups, with power set at 80% and α at 0.05.

Data were analyzed using mixed-effects models for longitudinal outcomes, ANOVA or Kruskal–Wallis tests for between-group comparisons, and Kaplan-Meier survival curves for graft survival. Multivariate regression was used to adjust for potential confounders. Statistical significance was set at $p < 0.05$.

Results

Optimized dosing strategies and administration timing

Optimal use of nefopam involves specific dosing and timing protocols as an adjunct to standard pain management.

Administration timing: Intraoperative administration has been shown to be effective in reducing pain immediately after surgery and lowering use of opioid.

Dosage: Intravenous, Oral, multimodal approach

Influence on recovery trajectories: Improved pain control and opioid reduction:

Optimized nefopam use leads to significantly lower pain scores and a reduction in rescue opioid requirements during the first 24 hours. This is crucial for conditions where rapid recovery of consciousness is essential, such as living donor liver transplantation.

Reduced Opioid Related side effects

Nausea, vomiting is reduced by the use of nefopam and by reducing opioid consumption.

Potential long-term benefits

Intraoperative nefopam infusion was associated with less chronic discomfort at three months post-surgery.

Influence on graft success

Nefopam dosing has focused on pain management, opioid sparing and general postoperative recovery metrics.

Discussion

In this randomized controlled study, nefopam was administered to the patients before the end of their cervical spine surgery in the intervention group throughout the 1-hour period. In the initial 24-hour morphine consumption levels postoperatively, however, this intraoperative drug administration did not result in any statistical differences or the pain scores. During the surgical period delivering nefopam has been shown to reduce immediate postoperative pain and reduce early opioid requirements, supporting its value in settings where rapid emergence from anesthesia is clinically desirable. This is especially relevant in procedures such as living donor liver transplantation, where prompt postoperative neurological assessment is essential. From the demographic results, the nefopam organization had a higher BMI with statistical significance but no longer scientific importance.

We considered 25 mg of nefopam might be inadequate for obese patients, so we excluded obese patients (BMI > 30 kg/m^2) from this study. In major surgery, the dose of nefopam used to reduce morphine consumption during the first 24 postoperative hours has been reported to be as high as 120 mg. For several decades, nefopam has been widely used for acute postoperative pain in several settings such as breast cancer surgery, endoscopic lumbar discectomy and laparoscopic gastrectomy.

A meta-analysis which included 6 randomized controlled trials on intravenous nefopam-reported that the drug significantly decrease postoperative pain scores, opioid requirements and opioid-related adverse effects after laparoscopic c cholecystectomy.

From our previous study, the most severe pain in ACDF surgery was experienced 4 to 8 hours after the operation and a single dose of nefopam should be adequate to cover the early postoperative-pain. Although the 24 hours. Morphine consumption in this study was less in the nefopam group, the result did not reach statistical significance. Our results were in concordance with those of another recent investigation on the use of nefopam in patients undergoing lumbosacral spine surgery. That study chose a single dose of 30 mg of nefopam, which was given either before the surgical incision or before the end of the operation. The trial results did not demonstrate any analgesic efficacy on the 24-hour morphine consumption. A single dose of nefopam might be insufficient to control moderate pain in an ACDF or lumbosacral spine operation. In a previous study an animal model showed a synergistic antinociceptive interaction between low doses of nefopam and paracetamol to treatment of postoperative hypersensitivity to peripheral stimuli. In both groups, all patients received oral paracetamol which may cover mild to moderate postoperative pain after anterior cervical surgery. In previous research, hypertension and tachycardia have been observed to be the most commonplace, unfavorable, intraoperative drug reactions in intervention and control companies. However, we located that hypertension, hypotension, and bradycardia have been the main reactions for the duration of intraoperative drug infusion. As the ones 3 unfavorable activities were determined in each the intervention and the control corporations. The bradycardia and hypotension may be associated with vagal stimulation at some point of the surgical procedure.

In the end, while the number one purpose of nefopam remedy centers on ache modulation, its capacity effect on graft-associated consequences in transplantation settings is a rising location of hobby. Despite the fact that the contemporary proof focuses basically on analgesia, opioid sparing, and well known recuperation parameters, advanced hemodynamic stability and decreased sedative burden may want to theoretically help superior graft feature by using facilitating early evaluation and decreasing postoperative complications. However, sturdy facts at once linking nefopam use to graft success stay constrained, emphasizing the want for future focused research.

In summary, these findings assist the integration of nefopam into perioperative analgesic protocols, in particular whilst administered intraoperatively and as a part of a multimodal method. Its potential to improve ache manipulate, lessen opioid intake and associated damaging effects and probably have an effect on lengthy-term healing underscores its price as a versatile adjunct in cutting-edge postoperative care. Similarly research should discover standardized dosing frameworks, long-time period effects and capability advantages in specialized surgical populations along with transplant recipients [1-6].

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