doi.org/10.36721/PJPS.2026.39.12.16662.1

Efficacy and safety of opioid analgesia with hydromorphone combined with nalbuphine in patient-controlled intravenous analgesia following cesarean section: A retrospective cohort study

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Abstract: **Background**: Cesarean section serves as a widely employed surgical procedure in obstetric care. Intraoperative tissue trauma and postoperative uterine contractions are prone to cause moderate to severe acute pain. Effective postoperative analgesia can alleviate maternal suffering and promote physical recovery. Currently, strong opioids are widely used for postoperative intravenous analgesia, but the efficacy and safety of single drugs and multi-drug combinations for postoperative intravenous analgesia remain to be explored. **Objectives**: This study was conducted to assess the analgesic efficacy and safety of hydromorphone combined with nalbuphine versus hydromorphone monotherapy in patient-controlled intravenous analgesia (PCIA) following cesarean section, to optimize the analgesic protocol for clinical application. **Methods**: Based on retrospective medical records, parturients meeting the inclusion criteria were assigned to either the combination group (hydromorphone + nalbuphine, n=162) or the control group (hydromorphone alone, n=162) according to their postoperative PCIA regimens. Primary and secondary outcome indicators were compared between the two groups. Primary indicators included Visual Analog Scale (VAS) scores at 2 h, 6 h, 12 h, 24 h and 48 h postoperatively, as well as PCIA button-pressing times. Secondary indicators encompassed Ramsay Sedation Scale scores at 2 h, 6 h, 12 h, 24 h and 48 h postoperatively, the incidence of analgesia-related adverse reactions (such as nausea, vomiting, dizziness, pruritus and respiratory depression) and patient satisfaction levels. **Results**: The combination group achieved significantly lower VAS scores than the control group at all time points ($p \leq 0.001$), fewer PCIA presses ($p<0.001$) and slightly higher Ramsay Sedation Scale scores ($p<0.05$), all maintaining within 2-4 points (optimal sedation range). The incidence of common adverse reactions was markedly decreased (32.1% vs 50.0%, $p<0.001$) and the satisfaction rate was higher (82.7% vs 65.4%, $p<0.001$). **Conclusion**: Hydromorphone combined with nalbuphine exerts synergistic analgesic effects, with a lower incidence of adverse reactions and higher satisfaction. This optimized regimen is safe and worthy of clinical promotion.

Keywords: Cesarean section; Hydromorphone; Nalbuphine; Postoperative analgesia; Patient-controlled intravenous analgesia (PCIA)

Submitted 24-04-2026 – Revised 15-05-2026 – Accepted 15-06-2026

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INTRODUCTION

Over the past three decades, the global prevalence of cesarean delivery has been steadily increasing. China boasts the highest cesarean section rate in Asia, which climbed from 28.8% in 2008 to 34.9% in 2014 and further reached 36.7% in 2018 (Li *et al*., 2017; Li *et al*., 2020; Qiao *et al*., 2021). Postoperative pain is the most prevalent adverse experience among cesarean section patients, which can directly hinder maternal physical recovery, impair physical and mental health and disrupt the establishment of mother-infant emotional bonds and the successful implementation of breastfeeding (Duch *et al*., 2026; Wiezer *et al*., 2020; Li *et al*., 2025; Monks and Palanisamy, 2021).

Compared with other general surgical procedures, cesarean section requires higher-quality postoperative analgesia for specific reasons (Sangkum *et al*., 2021): Firstly, cesarean pain is complex, consisting of somatic incision pain and visceral spastic pain caused by uterine contraction (Chen *et al*., 2021). Secondly, postpartum parturients need to maintain clear consciousness to complete breastfeeding, mother-infant contact and early ambulation (Roofthooft *et al*., 2021). Thirdly, inadequate analgesia increases the risk of postpartum depression, venous thrombosis and poor uterine involution (Zhao *et al*., 2025; Federspiel *et al*., 2026; Wang *et al*., 2021).

Clinical data indicate that inadequate postoperative analgesia after cesarean section leads to chronic pain in at least 5.0% of patients (Jin *et al*., 2016). In addition, unprompted control of severe postoperative pain can give rise to multiple adverse complications, such as venous thromboembolism, analgesic abuse or addiction and concurrently elevate the risk of postpartum depression (Rath *et al*., 2025; Jin *et al*., 2016; Mehraban *et al*., 2021; Wang *et al*., 2024; Ning *et al*., 2024; Sheng *et al*., 2024).

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Therefore, providing comprehensive postoperative pain management for cesarean section patients is crucial, as it confers significant health benefits to both mothers and infants. However, the trauma induced by cesarean section, combined with the administration of uterotonics postoperatively, collectively poses constraints to achieving optimal analgesic outcomes (Qiu *et al*., 2024). At present, there are no explicit clinical guidelines for postoperative pain management following cesarean section and most medical institutions still rely primarily on single-agent opioid analgesia. This strategy is liable to cause adverse reactions, including nausea, vomiting and pruritus, while often failing to provide adequate pain relief. These issues not only cause patient anxiety and insomnia but may also lead to poor uterine contraction, postpartum hemorrhage, venous thrombosis and other complications, thereby affecting postoperative recovery and breastfeeding and even increasing the risk of mother-infant separation (Roofthooft *et al*., 2021; Mehraban *et al*., 2021, 2024; Huang *et al*., 2020). Therefore, optimizing postoperative analgesic regimens to improve efficacy while reducing adverse reactions holds great clinical significance for enhancing the prognosis of cesarean section patients. As a commonly used postoperative analgesic technique, Patient-Controlled Intravenous Analgesia (PCIA) has been widely applied in pain management after cesarean section (Jun *et al*., 2023, Roofthooft *et al*., 2021; andziak *et al*., 2015) and serves as a key component of multimodal analgesia. This modality offers superior analgesic efficacy, higher patient satisfaction, shorter hospital stays and mitigates adverse impacts on pulmonary function (Jun *et al*., 2023; Roofthooft *et al*., 2021).

Hydromorphone is a semi-synthetic opioid analgesic that exerts its therapeutic effects primarily through agonism of μ-opioid receptors, with minor activity at δ-receptors (Spetea and Schmidhammer, 2021). Characterized by rapid onset and potent analgesic efficacy against somatic pain, hydromorphone has been extensively used in clinical practice for PCIA(Huang *et al*., 2020; Abi-Aad and Derian, 2025; Yang *et al*., 2019; Yang *et al*., 2018). Studies have confirmed that hydromorphone exhibits greater analgesic potency compared to morphine (Meissner *et al*., 2023; Li *et al*., 2024; Muzaurieta *et al*., 2025). Additionally, compared to sufentanil, hydromorphone achieves favorable postoperative analgesia in patients undergoing thoracic, orthopedic and other surgical procedures, facilitating accelerated postoperative recovery (Yan *et al*., 2018). However, similar to other opioids, hydromorphone carries a risk of dose-dependent adverse reactions, most commonly nausea, vomiting and pulmonary complications, which can adversely affect maternal postpartum recovery (Li *et al*., 2024; Yan *et al*., 2018; Wu *et al*., 2021; Nie *et al*., 2022; Pan *et al*., 2021). Furthermore, monotherapy with hydromorphone often fails to meet the ideal analgesic needs of cesarean section patients, primarily due to its limitations as a pure μ-opioid receptor agonist in relieving visceral pain induced by uterine contractions (Huang *et al*., 2020).

Nalbuphine is an opioid agonist-antagonist that mediates its analgesic and sedative effects mainly through agonism of κ-opioid receptors. The complementary pharmacological characteristics of the two drugs provide a theoretical basis for combined medication (Huang *et al*., 2020). Both basic experimental and clinical studies have demonstrated that κ-opioid receptor-targeting agents exhibit significantly superior efficacy in antagonizing visceral pain induced by chemical stimuli compared to opioids acting solely on μ-receptors (Liu *et al*., 2021; Ruan *et al*., 2022). Another study suggested that combining opioid agonist-antagonists with μ-receptor agonists in PCIA regimens not only addresses both visceral and somatic pain but also markedly mitigates the incidence of such adverse events as nausea, vomiting, respiratory depression and pruritus (Huang *et al*., 2020).

Currently, comparative studies on the efficacy and safety of hydromorphone combined with nalbuphine versus hydromorphone monotherapy in PCIA after cesarean section remain scarce. This retrospective study included 324 patients who underwent cesarean section, aiming to comprehensively explore and systematically compare the clinical analgesic effectiveness and safety profiles of the two analgesic intervention strategies.

MATERIALS AND METHODS

Study design

A retrospective cohort study was conducted, which was approved with a waiver of informed consent. All medical records and relevant patient information were anonymized prior to data analysis. This research was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of Huanghe Sanmenxia Hospital. Medical records of parturients who underwent cesarean section at Huanghe Sanmenxia Hospital between 13 April 2024 and 1 July 2025 were collected.

Inclusion and exclusion criteria

Inclusion criteria

(1) Age exceeding 22 years; (2) Physical status graded as Class Ⅱ–Ⅲ according to the American Society of Anesthesiologists (ASA, ASA represents the American Society of Anesthesiologists physical status classification, evaluating preoperative systemic physical condition) classification criteria; (3) Received cesarean section surgery with postoperative patient-controlled intravenous analgesia (PCIA) administered via hydromorphone monotherapy or hydromorphone-nalbuphine combination therapy; (4) Complete medical records, laboratory test results and follow-up data.

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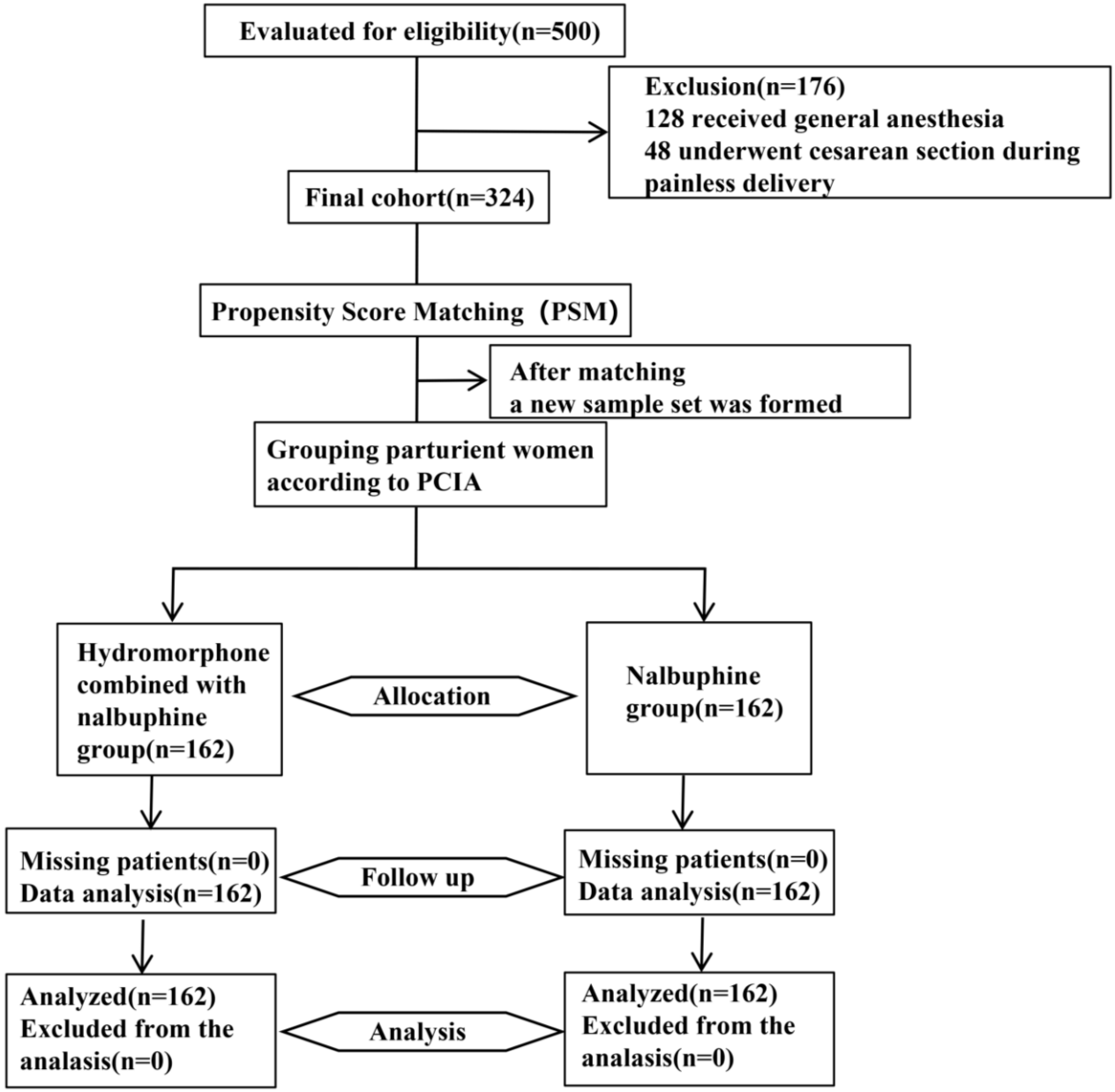


Fig. 1: The study flow diagram.

Exclusion criteria

(1) Received other analgesic modalities or multiple analgesic methods; (2) Converted from labor analgesia to cesarean section or or admitted to the intensive care unit (ICU) postoperatively; (3) History of allergies or hypersensitivity to opioids; (4) Language barriers or inability to communicate; (5) Missing data on the primary outcome indicator; (6) Presence of severe cardiovascular, hepatic, renal, respiratory, or neurological diseases. A schematic flowchart depicting the study protocol is presented in fig. 1.

Data extraction

The research was implemented in strict adherence to the ethical principles outlined in the Declaration of Helsinki. All study-related datasets were extracted from the clinical records archived in the hospital's electronic medical record system and no additional invasive operations or interventions were performed on patients. Prior to data collection and analysis, all personal identifiable information of patients was anonymized, including the deletion of names, hospitalization numbers, ID numbers and other identifiable information. Only clinical diagnosis and treatment data relevant to the study were retained to ensure that patient privacy was not compromised.

Anesthesia and analgesia methods

Clinical information was retrospectively retrieved from the hospital's Electronic Medical Record (EMR) system. Patients in both groups followed the routine preoperative

fasting and water deprivation procedure (documented in the preoperative evaluation record) and vital signs, encompassing electrocardiogram tracings, arterial blood pressure, cardiac rhythm and pulse oxygen saturation (SpO_2), were continuously monitored throughout the observation period. All patients received combined spinal-epidural anesthesia, with puncture performed at the lumbar $(L)_3$ –L_4 intervertebral space (L = lumbar; see anesthesia record). After successful puncture, 2–3 mL of 0.5% ropivacaine was intrathecally injected and the sensory block level was controlled below Thoracic $(T)_6$ (T = Thoracic, confirmed and documented by anesthetic nurses). During the operation, the infusion rate was adjusted according to changes in patients' vital signs and vasoactive drugs were administered when necessary to maintain circulatory stability (extracted from the intraoperative anesthesia record).

The PCIA pump was activated within the first 30 min after surgery and PCIA formulations were obtained from analgesic prescription records. The differential dosage design of hydromorphone in the two groups referred to the optimized PCIA dosage regimen for cesarean section reported in previous studies, which can effectively balance analgesic efficacy and safety of combined and single-agent opioid analgesia (Li *et al*., 2026, Schwenk *et al*., 2018). For the combined analgesia cohort, the PCIA mixture was composed of hydromorphone (0.1 mg/kg), nalbuphine (20 mg) and tropisetron (5 mg, Tropisetron is a 5-HT3 receptor antagonist widely used for postoperative antiemesis), which was further diluted with normal saline to reach a final volume of 100 mL. In contrast, the PCIA solution for the control group contained hydromorphone (0.2 mg/kg) combined with tropisetron (5 mg) and was likewise diluted with normal saline to a total volume of 100 mL. Uniform operational parameters were configured for all PCIA devices, as recorded in the electronic logs of the analgesic pumps: a loading dose of 1–3 mL, a background infusion rate of 2 mL/h, a patient - controlled bolus dose of 1 mL per demand and a lockout interval of 15 min. Both groups of patients received continuous PCIA for 48h postoperatively. The rescue analgesia protocol (documented in the postoperative nursing record) was defined as follows: if patients had a Visual Analogue Scale (VAS) score > 7 at any time point from T0 to T4 (T0-T3 represent postoperative time nodes: T0 = 2 h (hour), T1 = 6 h, T2 = 12 h, T3 = 24 h, T4 = 48 h, intravenous administration of flurbiprofen axetil (50 mg) was delivered as the rescue analgesic intervention when required.

Outcome measures

All outcome data were retrospectively extracted from electronic medical records (EMR), analgesic pump records and postoperative follow-up records. Referring to the common outcome evaluation framework for postoperative analgesia studies (Xue *et al*., 2022), the outcome measures were divided into primary and secondary indicators. Primary Indicators: (1) Analgesic efficacy: VAS scores at 2 h, 6 h, 12 h, 24 h and 48 h postoperatively were obtained from nursing assessment records to evaluate the pain intensity of parturients at different time points after surgery. The VAS score ranges from 0 to 10 points, with defined thresholds: 0 points denoted the absence of pain; scores ≤ 3 points represented mild, tolerable pain; scores of 4–6 points indicated moderate pain that disrupted sleep but remained bearable; and scores of 7–10 points corresponded to severe, intolerable pain that impaired both appetite and sleep quality. Notably, higher scores on this scale were indicative of more severe pain intensity(Alimy *et al*., 2023). (2) PCIA usage: Data on the total number of PCIA presses and the number of effective presses within 48 h postoperatively were obtained from the electronic records of the analgesic pump, to assess the parturients' demand for analgesics and the efficacy of the analgesic pump. Secondary Indicators: (3) Sedation efficacy: Ramsay Sedation Scale scores at each postoperative time point were extracted from Post-Anesthesia Care Unit (PACU) records and nursing records. The Ramsay score ranges from 1 to 6 points: 1 point indicates restlessness; 2 points indicate an awake and calm state; 3 points indicate drowsiness but arousable; 4 points indicate asleep but easily arousable; 5 points indicate somnolent and difficult to arouse; 6 points indicate coma. Scores of 2–4 points are considered the optimal sedation range (Yang *et al*., 2025). (*4*) Adverse reactions: By reviewing adverse reaction report forms and nursing records, the incidence of adverse reactions within 48 h postoperatively was statistically analyzed, including nausea and vomiting, dizziness, pruritus, urinary retention, respiratory depression (SpO_2 < 90%) and gastrointestinal discomfort (diarrhea/abdominal distension). (5) Patient satisfaction: Postoperative analgesic satisfaction at 48 h was obtained from follow-up questionnaire records, evaluated using a self-designed satisfaction scale. The satisfaction was classified into four grades: very satisfied, satisfied, neutral and dissatisfied. The case count and the corresponding percentage of participants in each satisfaction rating tier were computed. The overall satisfaction rate was derived from the following formula: [(count of highly satisfied participants + count of satisfied participants) ÷ total cohort size] × 100%

Statistical analysis

Retrospectively retrieved datasets were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 26.0. Propensity Score Matching (PSM) was implemented using the nearest-neighbor matching algorithm, with a caliper tolerance of 0.02. Following matching, the distribution. Normally distributed continuous Standardized Mean Difference (SMD) was used to assess baseline homogeneity of demographic and clinical characteristics between cohorts; an SMD < 0.1

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was considered indicative of satisfactory baseline balance. For continuous variables, the Kolmogorov–Smirnov normality test was first conducted to assess data were presented as mean ± standard deviation ($\bar{x}\pm s$), independent-samples t-test and were adopted for inter-group comparison at each single time point; Non-normally distributed continuous variables were expressed as median (interquartile range) [M (IQR)] and intergroup comparisons for such variables were performed using the Mann–Whitney U test. Categorical variables were recorded as numbers (percentages) [n (%)], and group-wise comparisons of these variables were executed via Pearson's chi-square test ($\chi 2$). To dynamically analyze the longitudinal changing trend of repeated measurement data, Linear Mixed Model (LMM) was applied, and the F-test was used to evaluate the main effect of group, the main effect of time point and the interaction effect. Given the multiple outcome measures in this investigation, the Bonferroni correction was used to adjust for multiple comparisons, thereby reducing the likelihood of Type I errors. A two-tailed *p*-value < 0.05 was defined as statistically significant.

RESULTS

Comparison of baseline data

A total of 500 patients undergoing cesarean section were initially screened, and 176 were excluded based on two criteria: (1) 128 patients received general anesthesia (not the combined spinal-epidural anesthesia focused on in the study); (2) 48 patients underwent cesarean section during labor analgesia (not conforming to the postoperative analgesia scenario of the study). After exclusions, the final research cohort comprised 324 eligible participants. To mitigate inter-group bias and control for potential confounding variables, a 1:1 nearest-neighbor PSM strategy was implemented with a caliper tolerance of 0.02, yielding a matched cohort for subsequent analyses. Using this matched sample set as the analytical basis, participants were stratified into two subgroups according to their respective PCIA regimens: the combined-analgesia group (n=162) and the control subgroup (n=162). As shown in table 1, after matching, Baseline characteristics (including age, gestational age, body weight, ASA physical status classification and operation time) were well-balanced between groups ($p > 0.05$), confirming comparable cohorts.

Comparison of VAS scores

A Linear Mixed Model (LMM) was used to analyze the repeatedly measured postoperative Visual Analog Scale (VAS) scores (dependent variable: VAS score; fixed effects: group, time point and group ×time point interaction; random effect: individual patient intercept; covariates: age, body weight). The results were as follows: the main effect of group indicated that the overall VAS score of the combination group was significantly lower than that of the control group ($p<0.001$); the main effect of time point indicated that VAS scores in both groups decreased significantly over time ($p < 0.001$); the group×time point interaction effect indicated that there was a significant difference in the decreasing trend of VAS scores between the two groups ($p<0.001$). These findings suggest that the PCIA regimen of hydromorphone combined with nalbuphine can significantly reduce pain intensity across all postoperative time points after cesarean section, with a more favorable analgesic efficacy trend, reflecting the synergistic analgesic advantage of "opioid combination use" (nalbuphine can enhance the analgesic effect of hydromorphone). Details are shown in table 2.

Comparison of ramsay sedation scores

Taking Ramsay Sedation Scale score as the dependent variable, group (combination group/control group) and time point (2 h/6 h/12 h/24 h/48 h postoperatively) were included as fixed effects, individual patient intercept as the random effect and age and body weight as covariates. The results were as follows: the main effect of group indicated that the postoperative Ramsay Sedation Scale scores of the combination group were slightly higher than those of the control group ($p<0.001$), all within the safe range (2-4 points), with no cases of over-sedation (5-6 points) or under-sedation (1 point). The main effect of time point showed that Ramsay Sedation Scale scores in both groups decreased significantly over postoperative time ($p < 0.001$), reaching the highest at 2 h postoperatively (peak drug concentration), then gradually decreasing with drug metabolism and dropping to 2.2-2.3 points (awake state) at 48 h postoperatively, which was consistent with the pharmacokinetic characteristics of continuous PCIA drug infusion and metabolism(Yang *et al.*, 2025). Moreover, the decrease in score in the combination group was gentler, indicating a more stable state of sedation. The group ×time point interaction effect indicated a statistically significant difference in the temporal trend of Ramsay Sedation Scale scores between the two groups ($p<0.001$). Details are shown in table 3.

Comparison of PCIA press times

The total number of presses and effective presses reflect the postoperative pain demand of patients (fewer presses indicate more satisfactory pain control). Both indicators in the combination group were significantly lower than those in the control group ($p<0.001$), reflecting a synergistic analgesic advantage and reducing the frequency of patients' additional active drug administration.

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Table 1: Comparison of baseline data.

Variables	Combination group (n=162)	Control group (n=162)	Statistical value	*p* value
Continuous variables				
Age (years)	28.60 ± 3.50	28.20 ± 3.70	t=1.023	0.307
Gestational age (weeks)	39.20 ± 1.10	39.00 ± 1.20	t=1.356	0.176
Body weight (kg)	67.50 ± 5.80	68.10 ± 6.20	t=0.987	0.324
Operation time (min)	45.30 ± 8.60	46.10 ± 9.20	t=0.765	0.445
Categorical variables				
ASA physical status, n (%)			χ^2=0.348	0.555
Grade Ⅱ	140 (86.40)	143 (88.30)	-	-
Grade Ⅲ	22 (13.60)	19 (11.70)	-	-
Underlying diseases, n (%)			χ^2=0.512	0.474
Gestational hypertension	18 (11.11)	15 (9.30)	-	-
Gestational diabetes mellitus	12 (7.40)	14 (8.60)	-	-
No underlying diseases	132 (81.50)	133 (82.10)	-	-

Note: Continuous variables (Age, Gestational age, Weight, Operation time) were analyzed by independent-samples t-test; Categorical variables (ASA physical status classification, Underlying diseases) were analyzed by Pearson's chi-square test. SMD < 0.1 indicated good baseline homogeneity.

Table 2: Comparison of VAS scores.

Group	Sample size (n)	2 h postoperatively	6 h postoperatively	12 h postoperatively	24 h postoperatively	48 h postoperatively
Combination group	162	3.80±0.90	3.20±0.80	2.60±0.70	2.10±0.60	1.50±0.50
Control group	162	4.50±1.00	3.90±0.90	3.30±0.80	2.70±0.70	1.80±0.60
t value	-	6.237	6.892	7.514	5.983	4.126
p value	-	＜0.001	＜0.001	＜0.001	＜0.001	0.001
Main effect of group	F=311.445，p<0.001，η_p^2=0.315					
Main effect of time point	F=1701.71，p<0.001，η_p^2=0.006					
Group×time point interaction effect	F=5.739，p<0.001，η_p^2=0.007					

Note: h=hour

Table 3: Comparison of ramsay sedation scores.

Group	Sample size (n)	2 h postoperatively	6 h postoperatively	12 h postoperatively	24 h postoperatively	48 h postoperatively
Combination group	162	3.10±0.40	2.90±0.30	2.70±0.30	2.50±0.30	2.30±0.20
Control group	162	2.80±0.40	2.60±0.30	2.50±0.30	2.40±0.20	2.20±0.10
t value	-	6.142	7.215	5.837	3.291	3.012
p value	-	＜0.001	＜0.001	＜0.001	0.001	0.003
Main effect of group	F=289.352，p<0.001，η_p^2=0.298					
Main effect of time point	F=1562.480，p<0.001，η_p^2=0.005					
Group×time point interaction effect	F=6.214，p<0.001，η_p^2=0.006					

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The combination of hydromorphone and nalbuphine effectively controlled pain while reducing hydromorphone dosage, as evidenced by fewer presses, aligning with the clinical demand for "synergistic analgesia and dose optimization". Details are shown in table 4.

Comparison of postoperative adverse reactions

The overall incidence of postoperative adverse events in the combined-analgesia group was 32.1%, which was remarkably lower than the 50.0% observed in the control group (χ^2=11.864， p<0.001). Specifically, the rates of nausea and vomiting, dizziness and pruritus in the combined-analgesia group were significantly reduced compared with those in the control group (p<0.05), In contrast, no statistically significant disparities were detected in the incidences of urinary retention, gastrointestinal disturbances and respiratory depression between the two cohorts (p>0.05). All adverse events were alleviated following symptomatic interventions, including antiemetic and antiallergic treatments. Notably, no severe adverse events led to treatment discontinuation or unfavorable clinical outcomes. Detailed data are summarized in table 5.

Comparison of analgesic satisfaction

The overall satisfaction rate of the combined-analgesia group was 82.7%, notably higher than the 65.4% in the control group (χ^2=12.307, p<0.001). Specifically, the percentage of participants reporting "highly satisfied" in the combined-analgesia group was 46.3%, compared with 29.6% in the control group, a difference that was statistically significant (p＜0.001). This finding suggests that the combined analgesia regimen not only provides effective pain control but also maintains a relatively low incidence of adverse events, thereby enhancing maternal satisfaction. Detailed breakdowns are presented in table 6.

DISCUSSION

Based on the pharmacological characteristics of the two drugs, this study proposed that the combination of hydromorphone and nalbuphine might exert a synergistic analgesic effect. Meanwhile, this combined regimen could reduce the dosage of each agent, thereby lowering the risk of adverse reactions. The findings of this research validated the hypothesis that the continuous, statistically significant intergroup difference in VAS scores has important clinical relevance. The combination group maintained persistently lower pain intensity throughout the 48-hour observation period, especially during the peak pain period (2–24 h). The stable synergistic analgesia reduced PCIA bolus times and avoided the need for rescue analgesia. Mild pain effectively promoted early ambulation, gastrointestinal function recovery and lochia discharge, which accelerated maternal rehabilitation (Jiang *et al*., 2025; Liu *et al*., 2025; Shi *et al*., 2023). The visual analog scale (VAS) scores in the combination group at 2, 6, 12, 24 and 48 hours postoperatively were markedly lower than those in the control group. This indicates that the analgesic efficacy of hydromorphone combined with nalbuphine is significantly better than that of the single-drug therapy and its analgesic effect covers the period of peak early postoperative pain (2-24 h postoperatively). After a cesarean section, incision pain and uterine contraction pain overlap, resulting in high early pain intensity (Zhou *et al*., 2025). The combination group showed significant analgesic advantages as early as 2 h postoperatively, indicating that the combination of the two drugs could take effect quickly and effectively relieve postoperative acute pain. Meanwhile, this analgesic advantage persisted until 48 h postoperatively without obvious attenuation, indicating stable and long-lasting analgesic effects. In addition, the total number of PCIA presses and the number of effective presses in the combination group were significantly reduced. This result suggests that hydromorphone combined with nalbuphine for PCIA after cesarean section can relieve early postoperative pain more quickly and effectively, reducing patients' demand for additional analgesics, which is closely related to the synergistic analgesic effect of the two drugs.

The results of this study are highly consistent with the pharmacological characteristics of the drugs and directly confirm the synergistic analgesic mechanism of hydromorphone combined with nalbuphine. After combination, the two drugs produce a synergistic effect through complementary receptor actions (Zhang *et al*., 2025b), which can significantly improve the overall analgesic effect while reducing the single hydromorphone dose (previous studies have confirmed that the hydromorphone dose in the combination group is only half that in the control group), thereby successfully achieving the core clinical goal of "analgesic potentiation and adverse reaction attenuation". This is also the core mechanism for the superior analgesic effect and good safety of the combination group (Zhang *et al*., 2025a). The quality of postoperative pain control after cesarean section directly affects patients' postoperative activities, mother-infant interaction and overall rehabilitation process. Poor pain control can lead to patients reducing ambulation due to fear of pain, increasing the risk of complications such as deep vein thrombosis of the lower extremities and pulmonary infection and affecting patients' willingness to feed and care for newborns (Zhang *et al*., 2025a). The stable and potent analgesic efficacy demonstrated by the combination group can effectively reduce the pain at the incision site during patients' physical activities, laying a solid foundation for the smooth implementation of early postoperative ambulation, thereby accelerating the recovery of gastrointestinal peristalsis function and promoting the smooth discharge of lochia.

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Table 4: Comparison of PCIA press times.

Group	Sample size (n)	Effective presses (times, $\bar{x}\pm s$)	Total presses (times, $\bar{x}\pm s$)
Combination group	162	9.80±3.20	12.30±3.80
Control group	162	16.50±4.10	19.70±4.50
t value	-	13.892	14.268
p value	-	<0.001	<0.001

Table 5: Comparison of postoperative adverse reactions.

Adverse reactions	Combination group (n=162) [n (%)]	Control group (n=162) [n (%)]	χ^2 value	*p* value
Nausea and vomiting	28 (17.30)	46 (28.40)	6.732	0.009
Dizziness	15 (9.30)	27 (16.70)	5.148	0.023
Pruritus	8 (4.90)	19 (11.70)	6.451	0.011
Urinary retention	10 (6.20)	12 (7.40)	0.258	0.612
Respiratory depression	0 (0.00)	1 (0.60)	1.002	0.317
Gastrointestinal discomfort (diarrhea/abdominal distension)	5 (3.10)	7 (4.30)	0.398	0.528
Total adverse reactions	52 (32.10)	81 (50.00)	11.864	<0.001

Table 6: Comparison of analgesic satisfaction.

Satisfaction grade	Combination group (n=162) [n (%)]	Control group (n=162) [n (%)]	χ^2 value	*p* value
Very satisfied	75 (46.30)	48 (29.60)	12.307	<0.001
Satisfied	59 (36.40)	57 (35.20)	-	-
Neutral	25 (15.40)	45 (27.80)	-	-
Dissatisfied	3 (1.90)	12 (7.40)	-	-
Satisfaction Rate (%)	134 (82.70)	105 (65.40)	12.307	<0.001

At the same time, effective control of pain symptoms can not only significantly improve patients' postoperative sleep quality but also reduce pain-induced systemic stress responses, enhancing patients' postoperative physical and mental comfort and self-care ability. The above clinical benefits are highly consistent with the core purpose of Enhanced Recovery After Surgery (ERAS) for cesarean section, providing key clinical support for ensuring maternal and infant safety and promoting stable postoperative rehabilitation of patients (Stringer and Nabhan, 2021).

The rapid onset of hydromorphone can quickly relieve immediate postoperative pain, while the long-acting analgesic advantage of nalbuphine can maintain stability in postoperative pain management. The combination of the two can achieve complementarity and synergistic enhancement of analgesic effects(Zhang *et al*., 2025b). Meanwhile, the hydromorphone dose in the combination group is only half that in the control group. The weak μ-receptor antagonistic effect of nalbuphine can further inhibit the occurrence of adverse reactions, resulting in significantly lower incidences of nausea, vomiting, dizziness, pruritus and other adverse reactions in the combination group than in the control group. It is worth noting that no severe adverse reactions such as respiratory depression occurred in the combination group, indicating good safety of this combined analgesic regimen. In terms of sedative effect, the Ramsay Sedation Scale scores of the combination group at all postoperative time points were slightly higher than those of the control group, but the scores of both groups remained within the ideal range. This subtle difference in sedation depth possesses clear clinical significance. First, all enrolled parturients maintained ideal sedation levels without insufficient sedation or excessive sedation, indicating the safety of both analgesic regimens. Second, the mild elevation in Ramsay scores in the combination group effectively relieved postoperative anxiety and pain-induced agitation without suppressing the patient's conscious level. Third, the combination group demonstrated a smoother decline in sedation scores over time, which contributed to stable intraoperative and postoperative hemodynamic stability and sustained good mental status. Fourth, the preservation of clear and calm consciousness is particularly essential for puerperae to complete early postoperative ambulation, lactation and mother-infant interaction. Notably, no respiratory depression or other sedation-related adverse events were observed in either group, further confirming the clinical safety of this combined analgesic strategy(Yang *et al*., 2025, Krishna *et al*., 2024).

This result clearly indicates that the combined use of hydromorphone and nalbuphine can precisely regulate

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sedation intensity, which not only prevents patient restlessness and heightened pain perception from insufficient sedation but also eliminates severe risks such as respiratory depression and confusion from over-sedation. It is consistent with the core demand for sedation depth in patients after cesarean section—alleviating pain-related anxiety while maintaining clear consciousness to cooperate with nursing care and observe newborns. The trend showing that the sedation score peaked at 2 h postoperatively and returned to the awake state at 48 h in both groups suggests that 2 h postoperatively is the period with the strongest sedative effect and a key window for prevention and control of over-sedation risk. During this period, it is necessary to strengthen monitoring of patients' respiratory rate and level of consciousness to avoid respiratory depression caused by peak drug concentration. The gentler decrease in scores in the combination group indicates that its postoperative sedation state is easier to manage, which can reduce the frequency of nursing interventions due to fluctuations in sedative effect and improve postoperative nursing efficiency. Meanwhile, the awake state with scores dropping to 2.2-2.3 points at 48 h meets the demand for rapid recovery of patients after cesarean section, providing a safe guarantee for the implementation of rehabilitation measures such as early postoperative ambulation and mother-infant interaction. Patient satisfaction is an important indicator for evaluating the pros and cons of analgesic regimens (2024, Botea *et al*., 2023). The significantly higher analgesic satisfaction among patients in the combination group than in the control group further confirms the clinical advantages of the combined regimen, which better meets the analgesic needs of patients.

Limitations of the study

This study has several inherent limitations due to its retrospective single-center design: (1) Due to the small sample size and single-center nature of the research, the results may be subject to bias. Further verification is required through multi-center, large-sample prospective studies; (2) The follow-up duration was limited, with observations only focusing on the analgesic effect and safety within 48 hours after surgery, while long-term prognosis was not evaluated; (3) The optimal dosage ratio of the combined medication was not explored and subsequent dose gradient studies are required to optimize the regimen.

Future research directions

Future research can be carried out from the following aspects: (1) Further study the response of different populations (such as obese parturients and parturients with other diseases) to the hydromorphone combined with nalbuphine analgesic regimen to expand the application scope of the research results; (2) Explore the efficacy and safety of the combination of hydromorphone and nalbuphine with other adjuvant analgesic drugs or methods (such as non-steroidal anti-inflammatory drugs, nerve block) to further improve the postoperative analgesic effect of cesarean section and reduce the dosage of opioids and related adverse reactions.

CONCLUSION

This retrospective cohort study confirms that hydromorphone combined with nalbuphine for PCIA after cesarean section exerts a synergistic analgesic effect. It significantly reduces VAS scores and Ramsay Sedation Scale scores at all postoperative time points, decreases the total number of PCIA presses and effective presses, lowers the incidences of adverse reactions such as nausea, vomiting, dizziness and pruritus and improves analgesic satisfaction, without increasing the risk of severe adverse reactions like respiratory depression. This combined regimen is safe and effective and can be regarded as one of the preferred regimens for PCIA after cesarean section.

Acknowledgment

None.

Authors' contributions

Guangliang Ma, Gang Xu, Huiting Liu: Edited and refined the manuscript with a focus on critical intellectual contributions, provided substantial intellectual input during the drafting and revision of the manuscript; Yanwei Wang, Xiaobin Wu: Participated in collecting, assessing and interpreting the data, made significant contributions to data interpretation and manuscript preparation; Jiaqi Chen, Lili Zhao, Dan Pei: Developed and planned the study, performed experiments and interpreted results. All authors have read and approved the final manuscript.

Funding

Henan Zhongyuan Medical Science and Technology Innovation and Development Foundation (Project No.: ZYYC2505020204).

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval

This study was approved by the Ethics Committee of the Yellow River Sanmenxia Hospital (Approval No.: 20250306). This study was performed in adherence with the RECORD guidelines. See supplementary file for the RECORD checklist.

Conflict of interest

The authors declare no conflict of interest.

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