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CLINICAL TRIAL REPORT

Effective Dose of Epidural Hydromorphone for Analgesia Following Caesarean Section in Using Modified Dixon Sequential Method

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Background: A single dose of epidural hydromorphone has been suggested as an alternative method for providing analgesia after caesarean section (CS). Nevertheless, the optimal dosage of epidural hydromorphone for postoperative pain relief following CS has yet to be determined.

Methods: This trial included 30 singleton primiparous women undergoing scheduled caesarean delivery, who were recruited to determine doses of epidural hydromorphone using the modified Dixon sequential method. The initial hydromorphone dose was 0.75 mg, with adjustments based on the efficacy of the preceding participant's dose over 12 hours. Various parameters such as blood pressure, heart rate, respiratory rate, visual analog scale (VAS) pain score, postoperative adverse reactions, and patient satisfaction with analgesic effect were recorded at each time point. The VAS scores were categorized as positive (score >3) or negative (score ≤3). Participants received a single epidural injection of 0.2% ropivacaine 20 mg along with a study dose of hydromorphone. The median effective dose (ED50), 90% effective dose (ED90), and corresponding 95% confidence intervals (CIs) of hydromorphone with ropivacaine for analgesia after caesarean section were calculated using the probit method.

Results: The ED90 and ED50 in our population were 1.105 mg (95% CI: 0.825–2.324 mg) and 0.659 mg (95% CI: 0.434–0.883 mg), respectively.

Conclusion: Epidural hydromorphone can be safely used for postoperative analgesia in patients undergoing caesarean section, and the analgesic effect is satisfactory when the dosage is appropriate.

Keywords: hydromorphone, ropivacaine, caesarean delivery, postoperative analgesia, ED50, ED90

Introduction

Caesarean section (CS) is often associated with intense postoperative pain and uterine contractions.[1] It is essential to offer women effective pain management options with minimal side effects to help speed up or support their recovery from surgical pain.

Epidural administration is considered an important analgesic technique for caesarean delivery, offering better postsurgical pain relief and fewer side effects when compared to intravenous analgesia.[2] Research has demonstrated the clinical effectiveness of epidural opioid analgesics in providing post-caesarean analgesia.[3] However, a long-term indwelling epidural catheter use is also a risk factor for catheter occlusion, catheter migration, or infection. Therefore, it is of great significance to explore single epidural administration for postoperative analgesia.

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Morphine, the most commonly used opioid, has been proven to be an effective drug with long-lasting effects following epidural administration.[4] While a single epidural injection of morphine can provide successful postoperative analgesia, it is associated with long-term opioid side effects.[5] Hydromorphone, a semisynthetic derivative of morphine, is extensively utilized for managing clinical pain.[6] It offers analgesic effects comparable to morphine but with the added benefit of reducing postoperative itching.[7] Studies have shown its efficacy in providing analgesia after caesarean section when administered epidurally.[8–10] Though epidural hydromorphone provides fast onset and modest duration of action clinically,[11] there are few data on the efficacy of its analgesia after CS. While the dose of 0.6 mg has been reported to reduce the dosage of sufentanil after CS,[12] the single optimal dose is still unknown. The purpose of this study is to determine the median effective dose (ED50) and 90% effective dose (ED90) of epidural hydromorphone in patients undergoing CS.

Materials and Methods

Study Design

This study was approved by the Ethics Committee of Nanjing Women and Children's Healthcare Hospital (Project number: 2022KY-127, review date: 2022–11-22), the research protocol was registered in the Chinese Clinical Trial Registry (Registration no.: ChiCTR2300070589). Subjects who were enrolled provided informed written consent. The single-center study was conducted at the Nanjing Women and Children's Healthcare Hospital, from which clinical data was collected.

Modified sequential therapy was used for this study. We set the initial epidural hydromorphone dose at 0.75 mg, and the ratio of adjacent doses was 1: 1.2–1: 1.5. Consequently, the effective dose gradient of hydromorphone (mg) was 0.1–0.2-0.3–0.4-0.5–0.75-1-1.5-2-2.5 by elevating four levels and reducing five levels of drug concentration on the basis of 0.75 mg, ten effective doses in total. The dosage of hydromorphone administered to each patient depends on the postoperative analgesia effect of the previous patient. If the result of the previous patient was "ineffective", then the hydromorphone dose escalation proceeded to the next. Otherwise, descend a gradient. We considered the analgesia to be effective if the VAS score of incision pain $\leqslant 3$ at 12 h after surgery, and conversely as ineffective.

Patients

All data were obtained from this study at Nanjing Women and Children's Healthcare Hospital between July 2023 and October 2023. The inclusion criteria of the subjects were as follows: A. Elective caesarean section, singleton pregnancy and primiparas. B. ASA grade 2, C. Birth $\geq$37 gestational weeks, age between 18 and 45 years old. D. No contraindications to intraspinal anesthesia.

Exclusion criteria consisted of the following: A. Participants who had participated in any other drug clinical trial within the prior 3 months. B. Participants who are taking or have taken non-steroidal anti-inflammatory drugs or opioids 48 h before surgery. C. Participants who had experienced skin pruritus. D. Participants with internal medicine comorbid conditions and hepatic and renal dysfunction before surgery. E. Patients with a change in anesthesia procedure. F. Participants with communication disorders and in poor compliance and could not complete the study protocol on schedule.

Anesthetic Procedure

Subjects were taken to the operating theater with intravenous access, ECG monitoring, and oxygen via a mask prior to anesthesia routinely. Then, the L3-L4 space was chosen for subarachnoid puncture with the patient in the left lateral position. The cerebrospinal fluid flow was unhindered following intravertebral puncture. Subsequently, a hyperbaric solution of ropivacaine (AstraZeneca AB, Naropin, London, England) (2.2–3 mL comprising 1% ropivacaine 2 mL and 5% glucose solution 1 mL) was administered at a rate of 0.2 mL/s with an indwelling epidural catheter. Commencement of the procedure would be initiated once the sensory block reached the T4 level. Lastly, different doses of hydromorphone (Yichang Humanwell, Hydromorphone HCI Injection, Wuhan, China) with 0.2% ropivacaine in 10 mL total were administered and the epidural catheter was removed postoperatively. And then immediately all subjects were maintained

on patient-controlled intravenous analgesia (PCIA) including 4 mg of hydromorphone, 8 mg of butorphanol tartrate (Jiangsu Hengrui Pharmaceuticals Co., Ltd., Butorphanol Tartrate Injection, Jiangsu, China) and 6 mg of granisetron (Ningbo Team Pharmaceuticals Co., Ltd., Granisetron Hydrochloride Injection, Zhejiang, China) dissolved in 100 mL of physiological saline. Parameters of the analgesic pump were set to no continuous dose, a single bolus dose of 3 mL and the lock-out duration 10 min every time. Pain of incision and other adverse effects, along with patient satisfaction, were noticed 24 h after the caesarean section.

Outcome Measures

Maternal general information, including name, age, height, weight, gravidity and parity, gestational week as well as diagnosis were noted immediately when enrolled. Pain of incision, other adverse effects, along with patient satisfaction was recorded 24h after caesarean section. We used a 10-point visual analog scale (VAS) to evaluate the pain intensity, ranging from 0 (No pain) to 10 (Worst imaginable pain). The primary outcome measure was ED90 of hydromorphone. The secondary outcome measures were the ED50 of hydromorphone; resting, moving, and contraction pain scores at 2, 6, 12 and 24 hours; blood pressure, heart rate, respiration rate and consumption of analgesic pump at each point of time; adverse reactions such as respiratory depression, nausea and vomiting, and itching; additional analgesic use; satisfaction of patients, postoperatively.

Statistical Analysis

SPSS (version 22.0, SPSS Inc., Chicago, IL, USA) and GraphPad Prism 8.0.0 (GraphPad Software, San Diego, CA, USA) were used to process the data statistically.[13–15] Normally distributed measurement data were represented by means ± standard deviation (SD) and compared between two groups (the positive vs the negative) using the Student's *t*-test. Non-normal distribution data were expressed as median (interquartile range [IQR]), and the statistics were conducted using Mann Whitney U rank sum test. The probit regression analysis method was used to calculate the ED50 and ED90 values of hydromorphone and their 95% confidence interval. We considered a p-value <0.05 that is statistically significant for the difference.

Results

A total of 30 patients participated in this study, and one participant was excluded due to the use of additional postoperative analgesic medication. Based on whether the VAS score was greater than 3 points 12 h after surgery, patients were stratified into an ineffective group and an effective group, that is negative or positive, respectively (Figure 1). Demographic data of the final 29 subjects included were presented in Table 1. From this table, there was no significant difference in demographic data, obstetric data, except for the dosage of hydromorphone.

The sequence of positive and negative reactions to hydromorphone for analgesia after CS is shown in Figure 2. The probit regression analysis yielded the equation Probit (P) = −2.366 + 3.592 × hydromorphone dose. A "goodness of fit test" with P = 1.629 > 0.05 suggested that the equation provided a strong fit for the data.

The ED90 and ED50 of hydromorphone in postoperative analgesia was 1.105 mg (95% CI: 0.825–2.324 mg) and 0.659 mg (95% CI: 0.434–0.883 mg) determined by using probit regression analysis, respectively (Figure 3).

The vital sign results of patients at 2 h, 6 h, 12 h, and 24 h after surgery are shown in Table 2, as well as the time from the end of surgery to the first use of patient-controlled analgesia. Overall, there is no statistical difference between the two groups of data.

We recorded the VAS scores on resting, moving and contraction at 2 h, 6 h, 12 h and 24 h after CS (Table 3). We found that patients in the negative group had significantly lower resting and moving pain scores at 6 h and 12 h, as well as moving pain scores at 24 h after surgery, compared with those in the positive group. These results indicated that reasonable hydromorphone dosage was of great significance in relieving postoperative analgesia in patients undergoing caesarean section.

There was a significant difference in the dosage of postoperative PCIA drugs between the two groups 12 h after surgery (Figure 4). The dosage of PCIA in the negative group was significantly reduced compared with the positive. The results showed that epidural hydromorphone could significantly reduce the use of postoperative analgesics in the effective group.

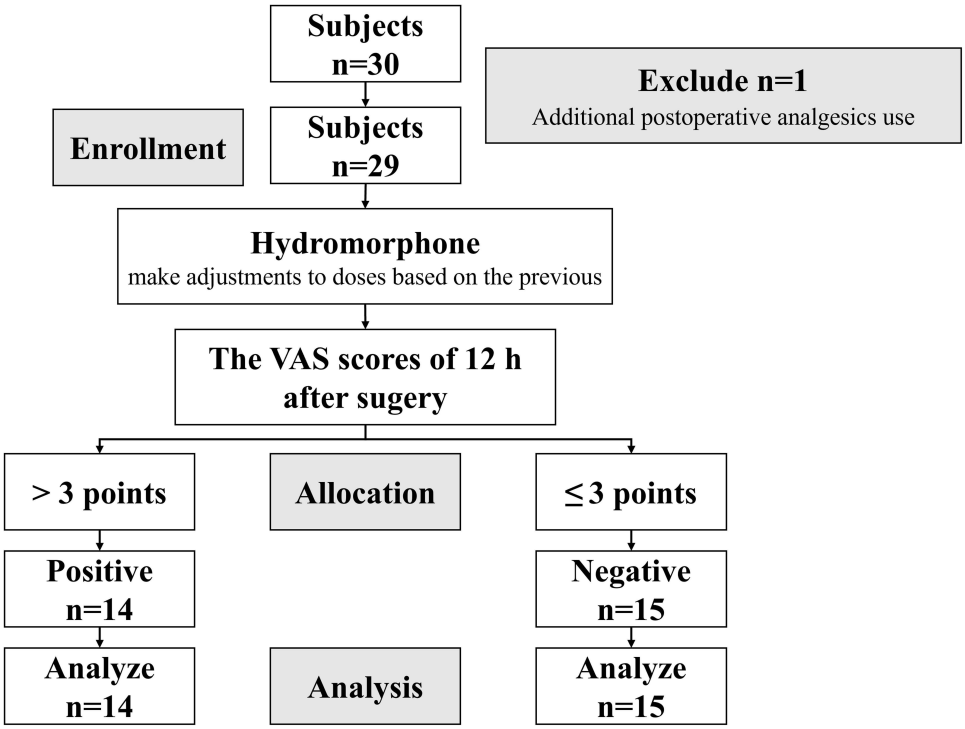

Figure 1 Study diagram showing enrolment, allocation and analysis.

No episodes of respiratory depression and headache were reported. The incidence of side effects such as dizziness, nausea, vomiting, and pruritus was not significantly different between the two groups.

Discussion

Caesarean section is the most common major surgery worldwide, and the rates continue to increase.[16,17] This means that pain after caesarean section is a common problem with significant health and economic consequences for both individual patients and society.[18] Appropriate management of pain after caesarean section is necessary to promote recovery, improve neonatal outcomes by increasing breastfeeding success and mother-infant bonding, and reduce pain-related side effects.[19]

For decades, long-acting opioids administered intrathecally or epidurally have been the mainstay of postoperative analgesia after caesarean section. Hydromorphone is a commonly used opioid for pain relief after caesarean section and has been shown to be effective as a first-line medicine.[20] Previous research found that epidural hydromorphone provided excellent caesarean analgesia.[8]

Table 1 Demographic Characteristics

	Positive	Negative	*p*-value
Age (years)	32.1±3.8	30.6±4.0	0.2992
Weight (kg)	73.5±12.2	69.5±9.7	0.3450
Height (m)	1.6±0.0	1.6±0.1	0.3653
Body mass index (kg/m^2)	27.2±3.7	26.4±3.6	0.5605
Gestational age (weeks)	39.1±0.4	39.3±0.5	0.1718
Hydromorphone dose (mg)	0.6±0.2	0.8±0.3	**0.0084**

Notes: Data are represented as Mean ± SD. Statistically significant results are bolded, two-sided *t*-test, $p < 0.05$.

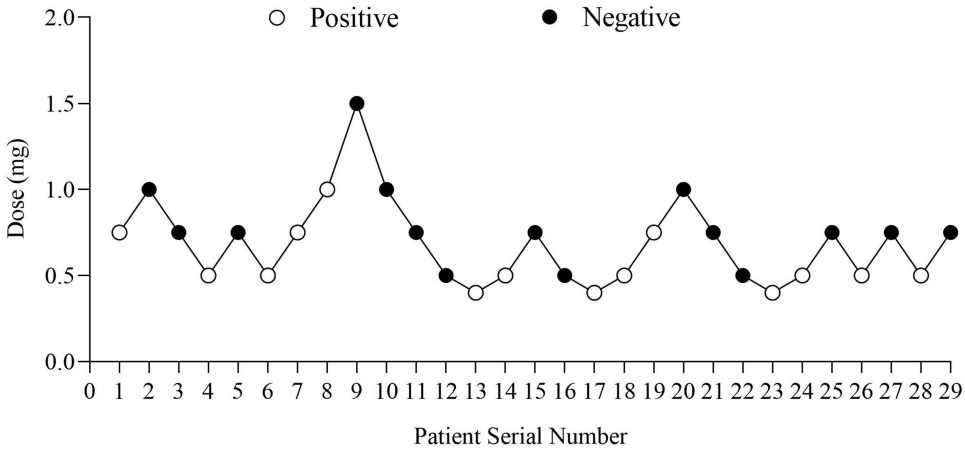

Figure 2 Sequence diagram of hydromorphone for analgesia after CS. Solid cycles represent negative reactions, while hollow cycles represent the positive.

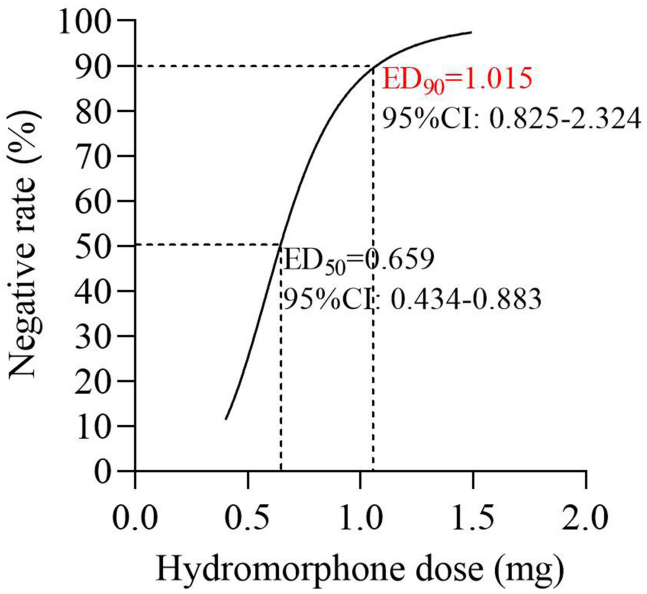

Figure 3 The dose–response curve of hydromorphone for analgesia after CS.

Chestnut et al compared single-dose epidural hydromorphone 1 mg with 0.25% bupivacaine 10 mL and found superior analgesia with hydromorphone post-caesarean delivery.[21] In addition, a study showed no significant differences in efficacy or side effects between epidural hydromorphone 0.6 mg and morphine 3 mg for post-caesarean section.[22] Studies have been conducted to establish the ED90 of intrathecal hydromorphone after caesarean delivery.[23] However, as a reliable alternative with high-quality postoperative analgesia and facilitating patient postoperative mobility, few prospective studies have been conducted to determine the ED50 or ED90 of single-injection epidural hydromorphone for analgesia after CS. Thus, we determined the ED50 and ED90 of epidural hydromorphone arm to evaluate the optimal dose after caesarean delivery.

This work determined the ED50 and ED90 of epidural hydromorphone for analgesia after CS, which was 0.659 mg (95% CI: 0.434–0.883 mg) and 1.015 mg (95% CI: 0.825–2.324 mg), respectively. We used a fixed stopping rule at the seventh inflection point, consistent with other studies using the modified up–down methods.[15]

Our results were similar to the previously reported doses of hydromorphone for post-caesarean section analgesia.[12] Yang et al explored the efficacy of single administration of epidural hydromorphone at different doses (0 mg, 0.2 mg, 0.4 mg or 0.6 mg) for analgesia after caesarean delivery. They found that a single epidural administration of 0.6 mg

Table 2 The Vital Sign Results at 2, 6, 12 and 24 h After Surgery

Patient Reporting Adverse Events		2 h	6 h	12 h	24 h
SBP (mmHg)	Positive (14)	119.0±11.5	112.6±9.5	111.1±7.1	113.3±11.5
	Negative (15)	114.7±8.1	117.3±12.6	110.8±8.8	113.1±20.3
	p-value	0.2550	0.2766	0.9093	0.9805
DBP (mmHg)	Positive (14)	75.4±6.4	72.8±7.8	70.7±5.6	72.1±8.9
	Negative (15)	71.1±9.1	70.3±5.6	68.2±6.1	67.9±8.7
	p-value	0.1648	0.3240	0.2589	0.2023
HR (bpm)	Positive (14)	74.6±12.0	83.4±12.4	82.1±13.2	81.9±14.1
	Negative (15)	70.9±8.8	84.0±13.5	81.5±12.8	81.1±10.6
	p-value	0.3406	0.9067	0.8896	0.8767
RR (breaths/minute)	Positive (14)	16.1±3.4	16.1±2.3	16.1±1.6	16.1±1.5
	Negative (15)	16.1±3.9	15.9±2.4	15.7±2.3	16.1±2.3
	p-value	0.9944	0.7561	0.6496	0.9409
		Time from the end of the operation			
First Bolus (min)	Positive (14)	476.3±259.8			
	Negative (15)	694.5±497.7			
	p-value	0.1549			

Notes: Data are represented as Mean ± SD. We consider 2-tailed $p < 0.05$ to indicate a statistically significant test result.

Table 3 The VAS Scores on Resting, Moving and Contraction at 2, 6, 12 and 24 h After CS

	Positive	Negative	*p*-value
2 h resting VAS score	0.0 (1.0)	0.0 (1.0)	>0.9999
2 h moving VAS score	0.0 (1.25)	0.0 (0.0)	0.2115
2 h contraction VAS score	0.0 (1.0)	0.0 (0.0)	0.1442
6 h resting VAS score	1.5 (2.0)	1.0 (2.0)	**0.0337**
6 h moving VAS score	3.0 (1.25)	2.0 (2.0)	**0.0027**
6 h contraction VAS score	1.0 (2.0)	0.0 (1.0)	0.0574
12 h resting VAS score	2.5 (2.25)	1.0 (2.0)	**0.0122**
12 h moving VAS score	4.0 (1.0)	2.0 (1.0)	**<0.0001**
12 h contraction VAS score	2.0 (3.0)	1.0 (1.0)	0.1229
24 h resting VAS score	3.5 (2.0)	2.0 (2.0)	0.1136
24 h moving VAS score	5.0 (0.5)	3.0 (3.0)	**0.0057**
24 h contraction VAS score	3.5 (3.25)	2.0 (4.0)	0.2053

Notes: Data are represented as median (IQR). Statistically significant results are bolded, Mann Whitney U rank sum test, $p < 0.05$.

hydromorphone achieved satisfactory analgesia, and the demand for auxiliary intravenous sufentanil was significantly reduced. However, the highest single dose of epidural hydromorphone was 0.6 mg, indicating that 0.6 mg may not be the optimal analgesic dose. Compared to Yang et al using VAS scores at different postoperative time points as the observation indicator, our observation indicators included VAS scores at different time points during rest, exercise, and uterine contractions. Any VAS score greater than 3 points was considered an analgesic failure. This evaluation method might be more rigorous and accurate in assessing the efficacy of epidural hydromorphone in parturient women. As the most sensitive part of the dose–response curve, small increments in ED50 level can produce significant changes in therapeutic efficacy.[24] The ED50 and ED90 of epidural hydromorphone derived from our research are expected to provide better guidance for post-caesarean section analgesia.

Although epidural opioids exhibit effective analgesic properties, they are also accompanied by common side effects. Our research indicated that there was no significant difference in the occurrence of adverse reactions between the two

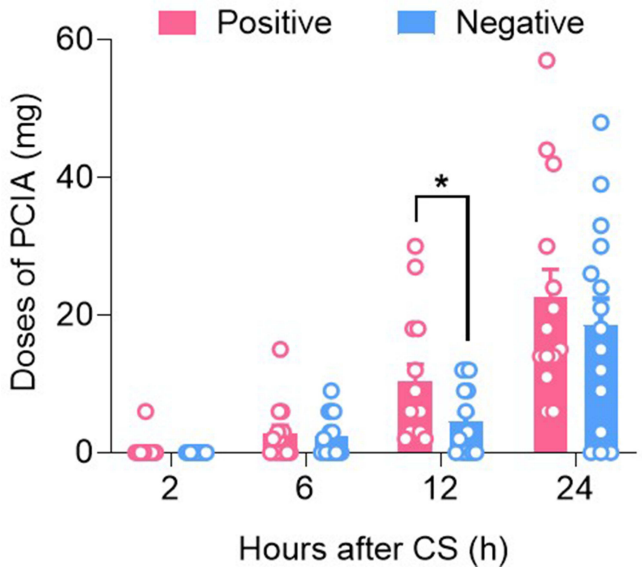

Figure 4 The dosage of postoperative PCIA drugs between the two groups at 2, 6, 12, 24 h after surgery. n = 14 samples for the positive and n = 15 for the negative group. *$p < 0.05$ versus the positive group, two-sided Student's *t* test.

groups. However, it was worth noting that the rate of adverse reactions to epidural hydromorphone might be increasing in correlation with the dosage administered. Marroquin's study revealed that approximately 25% of patients who received an epidural injection of 0.6 mg hydromorphone reported experiencing pruritus.[25] Additionally, Chestnut's research demonstrated that the incidence of skin itching reached as high as 58% when administering 1 mg of epidural hydromorphone.[21] Similarly, the study by Jonathan et al confirmed that the incidence of severe opioid-related events significantly increased by administering higher doses of intrathecal hydromorphone.[26] As a result, determining the appropriate dose of epidural hydromorphone could help reduce side effects, ensuring that patients received only the necessary minimum dose.

This study employed the Dixon sequential method to assess the ED50 and ED95 of hydromorphone, as it was a straightforward yet highly effective approach, requiring only a modest sample size. Cao et al utilized the up-down sequential allocation method to determine that the efficacy ratio of epidural morphine to hydromorphone for post-operative analgesia in hemorrhoid patients was 3:1. Furthermore, they calculated the ED50 for epidural hydromorphone analgesia within 24 hours post-hemorrhoidectomy to be 0.366 mg, resulting in a high level of patient satisfaction.[27] Our study referenced an effective dose of intrathecal hydromorphone with 75 μg in a single dose.[20] Based on the estimation that the epidural drug dose is approximately 10 times the subarachnoid space, 0.75 mg was selected as the starting dose of epidural administration. In this study, severe sedation and associated respiratory depression were not reported at any dose.

Limitations of the present study should be acknowledged. First, the patient population was exclusively of yellow ethnicity, potentially impacting generalizability to other racial groups due to variations in height, weight, and drug sensitivities. Secondly, the sample size was not large enough to draw firm conclusions about the relative side effects of hydromorphone, and additional verification was required to assess the efficacy and side effects of epidural hydromorphone. In summary, the study revealed that the ED50 and ED90 of epidural hydromorphone for post-caesarean section analgesia were 0.659 mg (95% CI: 0.434–0.883 mg) and 1.015 mg (95% CI: 0.825–2.324 mg) using a modified Dixon up-and-down sequential allocation method, respectively. When used as part of a multimodal analgesic approach, a single dose of epidural hydromorphone demonstrated effective pain relief and minimal side effects within the first 24 hours post-operation. Considering the current drug shortages, further exploration and recommendation of epidural hydromorphone are warranted.

Conclusion

Our research results indicate that epidural hydromorphone has a definite analgesic effect on postoperative pain in patients undergoing caesarean section. The estimated effective doses (EDs) obtained in this study will provide valuable guidance for clinicians when selecting the appropriate dosage of hydromorphone for post-caesarean section analgesia.

Abbreviations

CS, Caesarean Section; VAS, Visual Analog Scale; ED90, 90% Effective Dose, ED50, Median Effective Dose; PCEA, Patient-Controlled Epidural Analgesia, PCIA, Patient-Controlled Intravenous Analgesia.

Data Sharing Statement

Data and materials are available upon reasonable request. The original data in the manuscript are available upon request to the corresponding author.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Nanjing Women and Children's Healthcare Hospital (Project number: 2022KY-127, review date: 2022-11-22), the research protocol was registered in the Chinese Clinical Trial Registry (Registration no.: ChiCTR2300070589). Subjects who were enrolled provided informed written consent.

Consent for Publication

All participants signed consent to publish.

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Disclosure

The authors declare no conflict of interest.

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