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Effects of hydromorphone and morphine intravenous analgesia on plasma motilin and postoperative nausea and vomiting in patients undergoing total hysterectomy

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Abstract. – OBJECTIVE: To observe the effects of hydromorphone and morphine intravenous analgesia on plasma motilin and postoperative nausea and vomiting in patients undergoing a total hysterectomy.

PATIENTS AND METHODS: 80 patients who underwent hysterectomy from April 2015 to June 2016 were randomly divided into two groups, with 40 patients in each group. The two groups received an intravenous infusion of hydromorphone or morphine for analgesia. The VAS pain score and Ramsey sedation score were recorded 4, 8, 12, 24, and 48 hours after the first dose of analgesia. The scores of nausea and vomiting were recorded. The levels of motilin were determined by radioimmunoassay before anesthesia, after anesthesia, during hysterectomy and 1 day after the operation. The results showed that the analgesic effect of hydromorphone was more rapid than morphine.

RESULTS: There were significant differences in VAS scores between the two groups at each time point ($p<0.05$), indicating that the analgesic effect of hydromorphone was better than morphine's one. The scores of Ramsay sedation were less than 6 points at each time point within 48 hours after the operation. The content of plasma motilin in the hydromorphone group was higher than that in the morphine group during the first day after anesthesia. There were 34 cases (85%) of mild nausea and vomiting within 24 hours after the operation in the hydromorphone group. In the morphine group, there were 16 cases (40%) of mild nausea and vomiting within 24 hours after the operation, 10 cases (25%) of severe nausea and vomiting.

CONCLUSIONS: The occurrence of severe malignant vomiting after the use of morphine was more than that after the use of hydromorphone. Normal level and function of motilin is the basis of avoiding nausea and vomiting. Too fast or too slow gastrointestinal motility can induce postoperative nausea and vomiting.

Key Words
Hydromorphone, Morphine, Analgesia, Motilin, Hysterectomy.

Introduction

Morphine is a representative drug among opioids. It has long been used in cancer pain and postoperative analgesia, but morphine-induced nausea and vomiting are evident. The severity of nausea and vomiting and the significant dependence brings certain restriction to the clinical application; therefore, the search for morphine alternative products have become hot spots for the field of postoperative analgesia[1-3]. Hydromorphone is a derivative of morphine which belongs to partially synthesized opioid analgesic drugs. The main action site is the μ opioid receptor of the central nervous system[4]. Because of the changes in the molecular structure of hydromorphone, it is superior to the traditional analgesic drug, morphine, in terms of the clinical analgesic effect. Its drug dose is only 1/8-1/5 of morphine[5].

Hydromorphone is more advantageous than morphine for postoperative analgesia. Strictly designed randomized controlled clinical studies have also shown a significant reduction in the incidence of adverse reactions compared with morphine[6], but clinical studies of hydromorphone are still lacking in comprehensive information of different specialist surgery[7]. Motilin is a brain-gut peptide, mainly secreted by the small intestine, especially the chromaffin cells of the duode-

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num, into the intestinal cavity or blood[8,9]. Motilin has a significant and lasting promotion effect on the movement and electrical activity of gastric smooth muscle[10,11]. In general, motilin can induce or aggravate nausea and vomiting. To explore more about the role of hydromorphone and morphine in postoperative analgesia and postoperative adverse reactions, more clinical randomized controlled trials were needed to achieve greater analgesic efficacy, more safety, and fewer side effects. Therefore, in this study, we designed clinical trials according to the principle of randomized control to observe the effects of hydromorphone and morphine intravenous analgesia on plasma motilin and postoperative nausea and vomiting in patients undergoing total hysterectomy, and to explore the possible mechanism of gastrointestinal side effects, providing theoretical basis for the clinical application of analgesics.

Patients and Methods

Patients

80 patients underwent hysterectomy from April 2015 to June 2016 were selected in Xiangyang No.1 People's Hospital. They had no history of analgesia before surgery. Patients were divided into the hydromorphone group (n = 40) and the morphine group (n = 40) using the random number method. This study has been approved by the Medical Ethics Committee of Xiangyang No.1 People's Hospital. Before the analgesic treatment, the patients and/or their families have been informed of the possible efficacy and adverse reactions, and all signed the informed consent.

Inclusion criteria: (1) all patients met the indications of hysterectomy within the "modern hysterectomy guidelines"; (2) aged between 40 years old to 65 years old; (3) did not receive analgesic drug treatment for nearly 6 months before the investigation; (4) all patients signed the informed consent.

Exclusion criteria: (1) younger than 40 years of age or older than 65 years of age; (2) combined with various chronic pain patients; (3) tumor metastasis; (4) combined with inflammation, fever and/or cannot cooperate with the researchers; (5) abnormal or no behavior ability.

Methods

Grouping method: two groups of patients were given an intravenous infusion of morphine and hydromorphone analgesic. The intravenous hydromorphone and morphine dispensing process was performed by a research assistant and was double-blinded for both the surgeon and the patient.

Postoperative analgesic formula: the first dose for the hydromorphone group was 0.9% saline 5 ml + hydromorphone injection 0.4 mg, maintenance dose was 0.9% saline 100 ml + hydromorphone hydrochloride injection 3.6 mg, intravenous infusion pump drip rate was 2 ml/hour, continuous analgesia for 48 hours. The first dose of morphine group was 0.9% saline 5 ml + morphine hydrochloride injection 2 mg; the maintenance dose was 0.9% saline 100 ml + morphine injection 18 mg, intravenous infusion rate 2 ml/hour, continuous analgesia for 48 hours.

Test drug source: morphine hydrochloride injection, 10 mg/ml, Northeast Pharmaceutical Group, Shenyang Pharmaceutical Co., Ltd., SFDA Approval No. H21022436 (Liaoning, China). Hydrogenated morphine hydrochloride injection (Rui Ning), 2 mL (2 mg), Yichang Renfu Pharmaceutical Co., Ltd., SFDA Approval No. H20120100 (Hubei, China).

Indicators: VAS pain scores and Ramsey sedation scores were recorded 4, 8, 12, 24, and 48 hours after the first dose of analgesia, and adverse events such as nausea and vomiting were recorded. Nausea and vomiting score was performed, the time and extent of nausea and vomiting were recorded.

2 ml of fasting peripheral venous blood was obtained before and after anesthesia, during the hysterectomy and 1 day after the operation. The blood was placed in a centrifuge tube containing 30 μL of 10% EDTA and 30 μL of aprotinin, centrifuged at 4°C and 4000 rpm for 20 min; the supernatant was obtained and reserved at -20°C in a refrigerator. The content of motilin was determined by radioimmunoassay. Motilin immunoassay kit was provided by Beijing Furui Runkang Biotechnology Co., Ltd (Beijing, China).

Statistical Analysis

In this study, the data were analyzed and processed by SPSS20.0 statistical software (SPSS Inc., Chicago, IL, USA). The measurement data were expressed as mean ± standard deviation (x± s). A two-sample *t*-test was used for comparison between groups. The χ^2-test was used for comparison between groups for enumeration data; ANOVA was used for comparison between multiple groups and the post hoc test was SNK test. $p<0.05$ for the difference was defined as statistically significant.

Table I. Basic information of two groups (n = 40).

Group	Age (year)	Weight (kg)	Height (cm)	BMI (kg/m^2)
Hydromorphone	47.50±5.17	57.45±6.78	159.52±6.83	23.45±2.32
Morphine	49.50±5.55	56.12±6.01	163.37±6.39	23.39±2.47
t	1.1792	0.8243	1.8409	0.0792
p	0.2456	0.4149	0.0735	0.9373

Table II. Comparison of operation and anesthesia time ($\bar{x}$, n=40).

Group	Operation time (min)	Anesthesia time (min)
Hydromorphone	154±22	166±23
Morphine	171±30	184±31
t	2.0436	2.0854
p	0.0436	0.0438

Results

General Condition of Patients

80 patients undergoing elective total hysterectomy were included in this study with an average age of (48.50 ± 5.49) years. There was no significant difference between the hydromorphone group and the morphine group in terms of general condition (age, body weight, height, body mass index) (p>0.05) (Table I). The anesthesia time and the operation time were compared between the two groups. The operation time of the hydromorphone group was shorter than that of the morphine group (p<0.05), which indicated that the analgesic effect of hydromorphone was more rapid than that of morphine, and the analgesic effect was better (Table II).

Comparison of Postoperative Analgesia VAS Score

The analgesic VAS score was performed from 4 hours to 48 hours after the operation. The results showed that the VAS score was below 3 points at each time point for both groups, indicating that the analgesic effect of morphine and hydromorphone was good (p<0.05). The score of the hydromorphone group was better than that of the morphine group (p<0.05), indicating that the analgesic effect of hydromorphone was superior to morphine (Table III, Figure 1).

Comparison of Ramsay Sedation Score After Surgery

The Ramsay sedation score was performed between the two groups from 4 hours to 48 hours after the operation. The results showed that the Ramsay sedation scores were below 6 points at

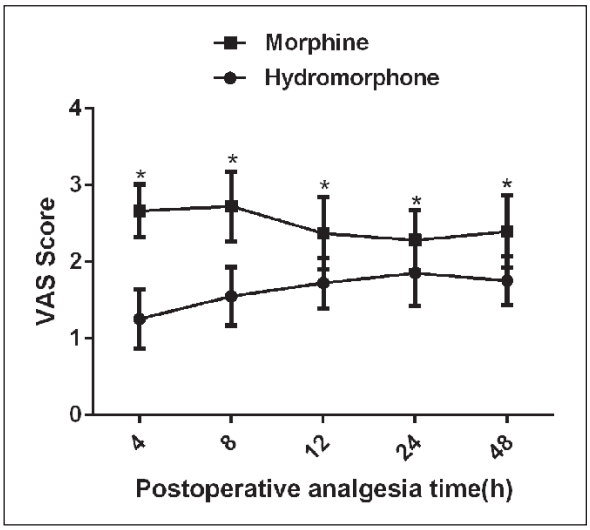

Figure 1. Comparison of analgesic VAS scores of both groups at each time point in 48 hours after the operation. Notes: *indicates that morphine group had a higher VAS score than that in hydromorphone group at the same time point, p<0.05.

Table III. Comparison of VAS scores of analgesia within 48 hours after surgery ($\bar{x}$, n=40).

Group	VAS score				
	4h	8h	12h	24h	48h
Hydromorphone	1.25±0.39	1.55±0.38	1.72±0.33	1.85±0.43	1.75±0.32
Morphine	2.66±0.35	2.72±0.45	2.37±0.47	2.28±0.39	2.39±0.47
t	12.0333	8.8838	5.0618	3.3126	5.0338
p	0.0000	0.0000	0.0000	0.0020	0.0000

Table IV. Ramsay sedation score within 48 hours after operation ($\bar{x}$, n=40).

Group	Ramsay sedation score				
	4h	8h	12h	24h	48h
Hydromorphone	1.25±0.39	1.95±0.78	4.42±0.13	4.85±1.01	5.75±1.17
Morphine	2.46±0.59	2.92±0.79	3.87±0.29	4.18±0.79	4.69±0.81
t	7.6512	3.9074	0.7773	2.3368	3.3313
p	0.0000	0.0004	0.4418	0.0248	0.0019

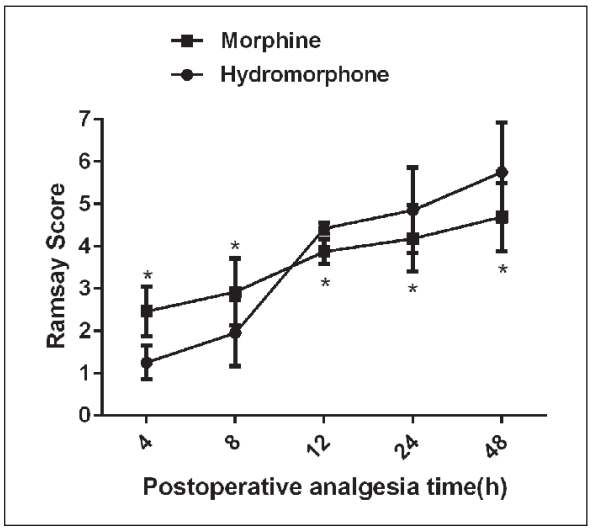

Figure 2. Comparison of Ramsay sedation scores at each time points at 48 hours after the operation. Morphine played a good sedative effect within 12 hours postoperatively, but the effect gradually weakened after 12 hours, while the sedative effect of hydromorphone was more lasting than that of morphine ($p<0.05$).
Notes: *, a statistically significant difference between two groups at the same time point ($p< 0.05$).

each time point, indicating that the sedative effects of morphine and hydromorphone were good. Comparison of the scores showed that morphine had a better sedative effect within 12 hours postoperatively, but the sedative effect was gradually weakened after 12 hours, while the sedative effect of hydromorphone was more lasting than that of morphine (Table IV, Figure 2).

Perioperative Plasma Motilin Content Comparison

There was no significant difference in plasma motilin levels between the two groups before anesthesia ($p>0.05$). The content of plasma motilin in the hydromorphone group was higher than that in the morphine group ($p<0.05$) from the end of the anesthesia to 1 day after the operation, indicating that the inhibitory effect of morphine on plasma motilin was stronger than that of hydromorphone (Table V, Figure 3).

The Occurrence of Nausea and Vomiting Within 24 Hours After Operation

There were 34 cases of mild nausea and vomiting (grade I-II) within 24 hours after operation in the hydromorphone group, accounting for 85% of the patients in this group. There was no serious nausea and vomiting (grade IV) in this group. In the morphine group, 16 patients occurred with mild nausea and vomiting (grade I-II) within 24 hours after the operation, accounting for 40% of patients in this group; 10 patients occurred with severe nausea and vomiting (grade IV), accounting for 25% of the patients. The results indicated that there were more severe malignant vomiting occurred after the use of morphine than that after the use of hydromorphone (Table VI, Figure 4).

Discussion

In recent years, postoperative intravenous analgesia has been widely used in clinical practice,

Table V. Comparison of perioperative plasma motilin levels (pg/ml, n = 40).

Group	Plasma motilin content (pg/ml)			
	Before anesthesia	After anesthesia	Hysterectomy	1 day after operation
Hydromorphone	332.25±40.39	361.95±40.78	438.12±55.13	471.85±61.44
Morphine	327.46±42.59	333.92±43.79	367.87±49.84	344.15±50.72
t	0.3855	2.0821	4.2116	7.1994
p	0.7020	0.0441	0.0002	0.0000

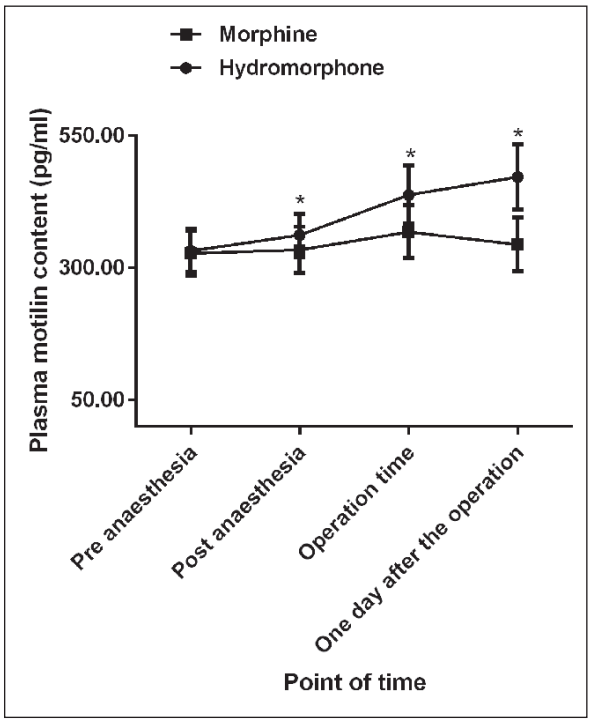

Figure 3. Comparison of perioperative plasma motilin levels in two groups of patients.
Levels of plasma motilin in the hydromorphone group were higher than those in the morphine group at all time points after anesthesia till 1 day after operation ($p<0.05$).
Notes: *, a statistically significant difference between two groups at the same time point ($p< 0.05$).

and multiple analgesic drugs have been developed. Zhu et al[12] suggested that the use of granisetron in combination with low-dose naloxone can effectively prevent nausea and vomiting after analgesia, and this combination can be well tolerated by patients, and the main adverse reaction was a headache with an incidence of about 10%. Other adverse reactions may occur, but special treatments are not needed. This combination has been widely used clinically to prevent adverse reactions that occur after analgesia. In this study, we used traditional opioids such as morphine and hydromorphone instead of newly developed analgesics such as tapentadol and fentanyl. The reason is that these traditional opioids are still widely used in China, and our findings may provide references for the use of those drugs. The affinity of pentamidine for its combination with MRO was weaker than that of morphine, and the analgesic effect was also poorer than that of morphine. Therefore, we selected morphine and hydromorphone based on the actual situations in China. To fully understand the adverse reactions caused by those two kinds of analgesics, antagonists were not used with the permission of patients and their families. The physiological processes of gastrointestinal motility are complex, involving myogenic, neurogenic, and chemical regulations[13,14]. These regulations are controlled by the hypothalamus, spinal cord, and gastrointestinal plexus, and are closely related with M receptors, μ receptors, and other sites[15]. Motilin is widely distributed in various parts of the central nervous system, such as the hypothalamus, hippocampus, spinal cord, midbrain, cerebellum, medulla oblongata, amygdala, spinal cord, etc. It also participates in gastrointestinal motility regulation[16]. Motilin acts as a ligand with its seven-layer transmembrane protein motilin receptor (GPR-38). It activates Gαq to increase its downstream MLCK expression, thereby activating phosphorylated MLC20 protein expression, while the increased expression of MLC20 can lead to the initial stage contraction of the gastrointestinal smooth muscle[17]. Morphine exerts its analgesic effect by acting on the opioid μ receptor located in the central nervous system.

Therefore, morphine will also have an impact on gastrointestinal motility while playing its analgesic effect, resulting in patients with nausea, vomiting, and other adverse reactions[18]. Since the amount of hydromorphone is less than morphine, intravenous morphine is more recommended for postoperative analgesia than morphine clinically. The analyzation in the changes of plasma motilin levels in the two groups showed that the inhibition

Table VI. The occurrence of nausea and vomiting within 24 hours after operation (n=40).

Group	Grading of nausea and vomiting			
	I	II	III	IV
Hydromorphone	18	16	6	0
Morphine	4	12	14	10
t		11.3403		
p		0.0100		

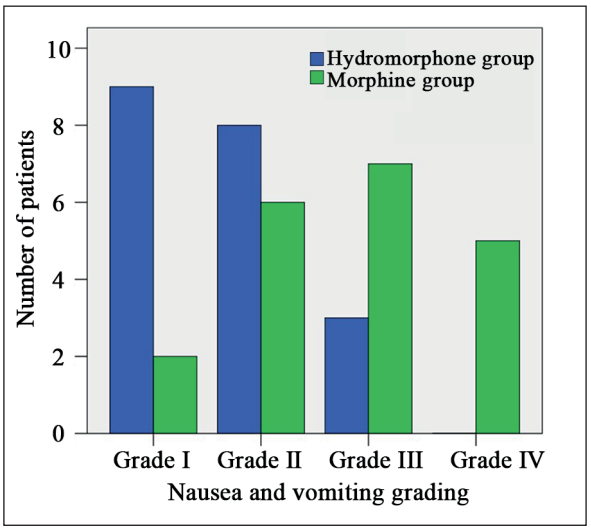

Figure 4. The occurrence of nausea and vomiting within 24 hours after the operation.

effect on plasma motilin of morphine was stronger than that of hydromorphone. However, we also found that the number of patients with severe nausea and vomiting after the use of morphine was significantly more than that of patients using hydromorphone. As the role of motilin is to maintain normal gastrointestinal motility, morphine has a strong inhibitory effect on plasma motilin. It is easy to cause slow gastrointestinal motility, gastrointestinal gas, and cause patients prone to nausea and vomiting[19].

Therefore, this work selected hydromorphone and morphine to study the plasma motilin and postoperative gastrointestinal adverse reactions of patients undergoing a total hysterectomy. By comparing the anesthesia time and operation time of the two groups ($p<0.05$), it was shown that the analgesic effect of hydromorphone was more rapid than morphine, hydromorphone could maintain better analgesic effect during operation. Postoperative intravenous analgesia of morphine and hydromorphone were good; analgesia VAS score was below 3 points at each time point. By comparing the VAS scores at each time point, it was found that the analgesic effect of hydromorphone was superior to that of morphine, and the role of hydromorphone in sedation was more durable. Ramsay sedation scores were below six points at each time point for both groups, indicating that the sedative effects of morphine and hydromorphone were good. The comparison between the scores showed that morphine played relatively good sedative effect within 12 hours postoperatively, but the sedative effect gradually decreased after 12 hours, while the sedative effect of hydromorphone was more lasting than morphine. The content of plasma motilin in the hydromorphone group was higher than that in the morphine group at all time points after anesthesia till one day after the operation. Patients with mild nausea and vomiting (grade I-II) within 24 hours after operation accounted for 85% of all the patients in the group, and there was no cases of severe nausea and vomiting (grade IV), while patients with severe nausea and vomiting (grade IV) accounted for 25% of the morphine group.

Since morphine/hydromorphone induced nausea/vomiting is dependent to dose, we didn't use other doses of morphine and hydromorphone. Moreover, the main assessment methods for assessing pain in patients receiving morphine and hydromorphone are still VAS pain scores and Ramsey sedation score. So we will try to solve these problems in our future studies.

Conclusions

We observed that the occurrence of severe malignant vomiting after the use of morphine was higher than that after the use of hydromorphone. Based on the results of this study and the physiological function analysis of motilin, it is possible to speculate that normal levels and functions of motilin are the basis for avoiding nausea and vomiting. Morphine and hydromorphone have a strong inhibitory effect on plasma motilin, which can cause slow gastrointestinal motility and therefore induce nausea and vomiting.

Competing interests:
The authors declare that they have no competing interests.

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