

Clinical Study of Preemptive Analgesia with Hydromorphone on Postoperative Analgesia in Patients with Laparoscopic Hysterectomy

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Lian *et al.*: Preemptive Analgesia with Hydromorphone in Laparoscopic Hysterectomy Patients

Pain after laparoscopic hysterectomy can lead to strong stress response, increase blood pressure and heart rate, restless during the awakening period. Preemptive analgesia is one of the methods to relieve postoperative pain. The purpose of this study is to explore the feasibility and safety of hydromorphone hydrochloride in preemptive analgesia, and to provide reference for clinical application. Two hundred American Society of Anesthesiologists I-II patients undergoing laparoscopic hysterectomy under endotracheal intubation general anesthesia from September 2019 to October 2020 were randomly divided into observation group (n=100) and control group (n=100) according to random number table. Patients in both groups were given intravenous rapid induction tracheal intubation combined with general anesthesia. 15 min before skin incision, hydromorphone hydrochloride 15 µg/kg (diluted to 10 ml with normal saline) was injected intravenously in the observation group, while normal saline 10 ml was injected into the control group. Visual analogue score was used to evaluate the analgesic effect after tracheal extubation. Venous blood samples were taken 5 min before anesthesia and after extubation, and the levels of plasma epinephrine, norepinephrine and dopamine were measured. The mean arterial pressure and heart rate of the two groups were recorded before anesthesia, after operation, immediately after extubation, 10 min after extubation and 30 min after extubation. Ramsay sedation scale was used to evaluate the sedation of patients with 10 min, 30 min and 1 h after endotracheal tube extubation. Riker Sedation-Agitation Scale was used to observe the occurrence of restlessness in the recovery period within 24 h after operation. There was no significant difference in basic characteristics between the two groups (p>0.05). Visual analogue score: compared with the control group, the visual analogue scores at 10 min after extubation, 30 min after extubation, 1 h, 2 h, 4 h, 6 h and 12 h after endotracheal tube extubation in the observation group were significantly lower than those in the control group. There was no significant difference in the levels of plasma epinephrine, norepinephrine and dopamine between the two groups before anesthesia. After extubation, the levels of plasma epinephrine, norepinephrine and dopamine in the 5 min control group were significantly higher than those in the observation group (p<0.05). Hemodynamics (mean arterial pressure and heart rate in the control group were significantly higher than those in the observation group after operation, immediately after extubation, 10 min after extubation and 30 min after extubation in mean arterial pressure and heart rate): groups, and the difference was statistically significant. There was no significant difference in spontaneous respiratory recovery time and extubation time between the two groups (p>0.05). Ramsay sedation score: there was no difference between the two groups. Preemptive analgesia with hydromorphone hydrochloride in patients undergoing laparoscopic hysterectomy under general anesthesia has good analgesic effect, less postoperative adverse reactions, and can effectively inhibit cardiovascular reactions during recovery.

Key words: Hydromorphone, preemptive analgesia, stress response, postoperative pain, emergence agitation.

In recent years, pain treatment drugs have also been developed rapidly, and rational use of drugs is an important link in pain treatment. Opioids have central and peripheral analgesic effects, and they are the most

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commonly used drugs for preemptive analgesia^[1]. Hydromorphone hydrochloride is a semisynthetic opioid, a derivative of morphine, which plays an analgesic effect by activating opioid receptors in the central nervous system. Hydromorphone hydrochloride was first synthesized in Germany in 1921 and used in clinic in 1926^[2]. It has a history of nearly 90 years, and entered the Chinese market in 2013^[3]. Hydromorphone hydrochloride has been used in clinic now. However, there are still great differences in our understanding of its efficacy, intensity and equivalent analgesic dose ratio with other opioids, and because of the ethnic differences of the drugs, the clinical efficacy and safety of the drugs may be affected by ethnic factors^[4]. The efficacy and side effects of the same drug and the same concentration on different races will be significantly different. At present, there are few studies on preemptive analgesia with hydromorphone hydrochloride, and the effect of preemptive analgesia with hydromorphone hydrochloride on postoperative acute pain needs to be further studied. Therefore, this study observed the effects of preemptive analgesia with hydromorphone hydrochloride on postoperative analgesia, cardiovascular reactions, stress reactions (epinephrine (E), norepinephrine (NE), dopamine (DA)), postoperative awakening and postoperative adverse reactions in patients undergoing laparoscopic hysterectomy under general anesthesia to provide clinical value for the reasonable and safe use of hydromorphone hydrochloride for preemptive analgesia.

MATERIALS AND METHODS

This study has been approved by the Medical Ethics Committee of our hospital, the purpose of the study has been explained to all patients, and the informed consent has been signed by the patients and their families. Two hundred patients, aged 45-65 y, weighing 45-70 kg and without cognitive impairment, were selected for laparoscopic hysterectomy in our hospital from September 2019 to October 2020. The patients were classified as American Society of Anesthesiologists (ASA) I~II by the American Association of Anesthesiologists. The patients were randomly divided into observation group (n=30) and control group (n=30). In the observation group, hydromorphone hydrochloride 15 µg/kg was injected intravenously before skin incision (normal saline was diluted to 10 ml) while in the control group, normal saline 10 ml was injected before skin incision. Exclusion criteria: patients with previous history of analgesic drug abuse and allergy, history of bronchial asthma and possible progression to

gastrointestinal obstruction were excluded. Withdrawal criteria: unexpected adverse events occurred suddenly, such as drug allergy, anesthesia and surgical accidents, changing the mode of operation, the need for a second operation, patients and their families asked to withdraw, and so on. The informed consent form of anesthesia was signed with the patient before anesthesia. All patients were evaluated and performed by the same anesthesiologist. The surgeon came from the same medical group, the abdominal pressure was 13-14 mmHg, and the operation time was within 90 min. The patients in the two groups were visited by the same anesthesiologist before anesthesia, ASA grade I~II, routine fasting for 8 h and drinking 6 h before entering into the operating room after routine oxygen inhalation (2.5 l/min). The observation group received intravenous injection of hydromorphone 15 µg/kg (diluted to 10 ml with normal saline) before skin incision, and the control group received normal saline 10 ml before skin incision. The effect of postoperative analgesia was evaluated by visual analogue scale (VAS) at 10 min after extubation (T4), 30 min after extubation (T5), 1 h (T6), 2 h (T7), 4 h (T8), 6 h (T9), 12 h (T10) and 24 h (T11) after endotracheal extubation. The plasma levels of stress hormone E, NE and DA were measured before anesthesia and after tracheal tube extubation by 5 min. The mean arterial pressure (MAP) and heart rate (HR) of patients before anesthesia (T1), after operation (T2), during extubation (T3), T4 and T5 were recorded. The recovery time of spontaneous breathing, extubation time (the time from the end of suture skin to extubation of endotracheal tube) and the time of operation (from the beginning of skin incision to the end of suture skin) were observed and recorded. After extubation, T4, T5 and T6 were evaluated by Ramsay score. Detection of plasma stress hormones (E, NE, DA): 4 ml of elbow venous blood was drawn at the time of admission and 5 min after endotracheal extubation in the two groups, and the venous blood drawn twice from each patient was packed and numbered sequentially. The contents of plasma stress hormones (E, NE, DA) were simultaneously determined by high pressure liquid chromatography with electrochemical detection. All the data were statistically analyzed by Statistical Package for the Social Sciences (SPSS) 19.0 software, the counting data were analyzed by X² test, the mean±standard deviation ($\bar{x}\pm s$) as used to represent the measurement data, the T test was used to compare the two groups of measurement data, and the analysis of variance was used to compare the multi group measurement data.

RESULTS AND DISCUSSION

Comparison of general conditions: there was no significant difference in sex, age, body weight and operation time between the two groups ($p>0.05$), as shown in Table 1. In the observation group, the age of the patients was 45.33 ± 64.03 y old, the average age was (50.53 ± 7.85) y, the body weight was $48.5\sim 67.8$ kg, the average weight was (53.53 ± 8.67) kg, the operation time was $76\sim 90$ min, and the average operation time was (78.20 ± 11.69) min. In the control group, the age was 46.65 to 63.79 y old, the average age was (52.07 ± 8.12) y, the body weight was 46.5 to 68.5 kg, the average weight was (56.14 ± 6.97) kg, the operation time was 74 to 90 min, and the average operation time was (80.80 ± 9.07) min (Table 1).

Comparison of analgesia scores (VAS) between the two groups at each time point: compared with the

control group, the VAS score of the observation group decreased significantly at T4, T5, T6, T7, 8, T9 and T10, but there was no significant difference between the observation group and the control group at T11. There was no significant difference between the two groups ($p>0.05$) (Table 2).

Comparison of the levels of stress hormones (E, NE, DA) between the two groups at each time point: compared with pre anesthesia and post extubation, the levels of plasma E, NE and DA; in 5 min of observation group and control group increased 5 min after extubation, the levels of plasma E, NE and DA in observation group increased 5 min after extubation, and the levels of E, NE and DA in control group increased 5 min after extubation. There was no significant difference in the levels of plasma E, NE and DA between the two groups before anesthesia. After extubation, the levels of plasma E, NE and DA in the 5 min control group were

TABLE 1: GENERAL CHARACTERISTICS OF THE PATIENT

| Groups | Cases | Age | Weight (kg) | Operation time (min) |
|-------------------|-------|-----------------|-------------------|----------------------|
| Observation group | 100 | 50.53 ± 7.85 | $48.55\sim 67.68$ | 78.20 ± 11.69 |
| Control group | 100 | 52.07 ± 8.12 | $46.35\sim 68.56$ | 80.80 ± 9.07 |
| χ^2 | / | / | / | / |
| t | / | -0.653 | 0.763 | -0.621 |
| p | 0.743 | 0.467 | 0.552 | 0.550 |

TABLE 2: THE VAS ON DIFFERENT TIMES AFTER OPERATION OF THE TWO GROUPS ($\bar{x}\pm S$, n=100)

| VAS core points | Observation (n=100) | Control (n=100) | t | p |
|-----------------|---------------------|-----------------|-------|--------|
| T4 | $1.09\pm 1.02^*$ | 4.27 ± 0.96 | 10.56 | <0.001 |
| T5 | $1.47\pm 1.06^*$ | 4.47 ± 0.89 | 10.96 | <0.001 |
| T6 | $2.08\pm 0.91^*$ | 4.46 ± 0.86 | -8.73 | <0.001 |
| T7 | $2.13\pm 0.75^*$ | 4.58 ± 0.76 | -9.08 | <0.001 |
| T8 | 5.78 ± 0.63 | 4.72 ± 0.69 | -9.85 | <0.001 |
| T9 | $4.04\pm 0.65^*$ | 5.78 ± 0.63 | -8.04 | <0.001 |
| T10 | $2.56\pm 0.91^*$ | 3.43 ± 0.74 | -5.86 | <0.001 |
| T11 | 1.81 ± 0.64 | 2.06 ± 0.56 | -1.31 | 0.23 |

Compared with control group, * $p<0.05$

TABLE 3: THE PLASMA E, NE AND DA BEFORE ANESTHESIA AND 5 MIN AFTER EXTUBATION OF THE TWO GROUPS ($\bar{x}\pm S$, n=100, pg/ml)

| Stress hormone | Observation group | Control group | t | p |
|------------------------|------------------------|---------------------|--------|-------|
| E Before anesthesia | 43.81 ± 10.96 | 47.82 ± 13.57 | -0.865 | 0.425 |
| After extubation 5 min | $92.56\pm 25.54^{*#}$ | $124.67\pm 63.68^*$ | -2.549 | 0.021 |
| t | -10.034 | -5.568 | / | / |
| p | <0.001 | <0.001 | / | / |
| NE Before anesthesia | 235.60 ± 24.42 | 345.19 ± 38.42 | -1.396 | 0.179 |
| After extubation 5 min | $373.88\pm 90.51^{*#}$ | $433.33\pm 86.02^*$ | -2.608 | 0.012 |
| t | -5.577 | -9.345 | / | / |
| p | <0.001 | <0.001 | / | / |
| DA Before anesthesia | 56.62 ± 11.79 | 52.94 ± 9.89 | -0.421 | 0.687 |
| After extubation 5 min | $73.44\pm 21.87^{*#}$ | $94.23\pm 50.06^*$ | -2.565 | 0.021 |
| t | -4.450 | -4.267 | / | / |
| p | <0.001 | <0.001 | / | / |

Compared with before anesthesia, * $p<0.05$; Compared with control group, # $p<0.05$

significantly higher than those in the observation group (Table 3).

Comparison of MAP and HR between the two groups at each time point; Compared with T1, MAP in MAP group increased at T2, T3, T4 and T5 in observation group, and MAP in control group increased at T2, T3, T4 and T5 compared with T1. In HR group, compared with T1, HR increased at T2 and T3 in observation group, but there was no significant difference in HR at T4 and T5. Compared with T1, HR in control group increased at T2, T3, T4 and T5, and there was significant difference between control group and control group at T2, T3, T4, T5. Comparison between groups: there was no significant difference in MAP and HR between the two groups at T1 time point, but the other T2, T3, T4, T5 time points in the control group were significantly higher than those in the observation group ($p < 0.05$) (Table 4 and Table 5).

Comparison of spontaneous respiratory recovery and extubation time between the two groups; There was no significant difference in the recovery time of spontaneous respiration between the observation group and the control group ($p > 0.05$), and there was no significant difference in the time of tracheal extubation between the two groups ($p > 0.05$) (Table 6).

Comparison of sedation score (Ramsay score) between the two groups at each time point; Compared with the

control group, there was no significant change in Ramsay sedation score at T4, T5 and T6 in the observation group, and there was no significant difference between the two groups ($p > 0.05$) (Table 7).

In this study, the intravenous dose of hydromorphone hydrochloride was 15 $\mu\text{g}/\text{kg}$, which was equivalent to 0.1 $\mu\text{g}/\text{kg}$ sufentanil. The results showed that preemptive analgesia with hydromorphone hydrochloride could significantly reduce the VAS score and the incidence of restlessness after laparoscopic hysterectomy^[5], indicating that it can effectively relieve surgical injury and visceral traction stimulation caused by CO_2 pneumoperitoneum, and reduce postoperative pain. It can also improve the tolerance of patients to endotracheal tube and reduce the incidence of restlessness caused by early postoperative pain. Yan Guosheng^[6] found that epidural injection of hydromorphone hydrochloride before the end of cesarean section can effectively relieve postoperative acute pain. Ouyang Yinghui^[7] also found that intravenous injection of hydromorphone hydrochloride before operation can also reduce the occurrence of restlessness during postoperative recovery, which supports the results of this study. Daniel P^[8] also found that intranasal administration of hydromorphone hydrochloride within 10-15 min can relieve pain in most patients, which can be used as a rapid method to relieve acute pain. Scott^[9] and other clinical studies found that there was a significant positive correlation between

TABLE 4: THE MAP ON DIFFERENT TIMES OF THE TWO GROUPS ($\bar{x} \pm S$, $n=100$, mm/Hg)

| Time | Observation group | Control group | t | p |
|------|-------------------------|--------------------------|--------|--------|
| T1 | 82.45+6.34 | 84.78+6.23 | -1.532 | 0.275 |
| T2 | 94.60+5.43 [#] | 97.22+5.41 [*] | -2.235 | 0.025 |
| T3 | 96.07-8.56 [#] | 114.70+7.38 [*] | -7.562 | <0.001 |
| T4 | 92.27+4.90 [#] | 102.40+7.56 [*] | -6.567 | <0.001 |
| T5 | 73.56+7.23 [#] | 85.56+5.67 [*] | -5.419 | <0.001 |

Compared with T1, ^{*} $p < 0.05$; Compared with control group, [#] $p < 0.05$

TABLE 5: THE HR ON DIFFERENT TIMES OF THE TWO GROUPS ($\bar{x} \pm S$, $n=100$, times/min)

| Time | Observation group | Control group | t | p |
|------|-------------------------|-------------------------|--------|--------|
| T1 | 72.53+5.06 | 72.75+7.02 | 1.597 | 0.121 |
| T2 | 82.55+6.63 [#] | 83.24+8.01 [*] | -2.461 | 0.008 |
| T3 | 82.35+6.01 [#] | 91.67+6.29 [*] | -5.112 | <0.001 |
| T4 | 74.64+6.91 [#] | 80.35+6.77 [*] | -3.432 | <0.001 |
| T5 | 71.46+8.03 [#] | 81.45+5.65 [*] | -5.332 | <0.001 |

Compared with T1, ^{*} $p < 0.05$; Compared with control group, [#] $p < 0.05$

TABLE 6: THE RESULTS OF SPONTANEOUS BREATHING RECOVERY TIME AND EXTUBATION TIME OF THE TWO GROUPS ($\bar{x} \pm S$, $n=100$, min)

| Group | Cases | Recovery time of spontaneous breathing | Extubation time |
|-------------------|-------|--|-----------------|
| Observation group | 100 | 4.07±0.68 | 5.67±0.67 |
| control group | 100 | 4.58±0.67 | 5.54±0.86 |
| t | / | 0.254 | 1.233 |
| p | / | 0.754 | 0.235 |

TABLE 7: THE RAMSAY SCORE ON DIFFERENT TIMES AFTER OPERATION OF THE TWO GROUPS (x±S, n=100)

| Group | Cases | T4 | T5 | T6 |
|-------------------|-------|-----------|-----------|-----------|
| Observation group | 100 | 2.45±0.45 | 1.87±0.16 | 2.23±0.25 |
| Control group | 100 | 1.89±0.42 | 1.96±0.31 | 1.95±0.34 |
| t | / | 1.104 | 1.027 | 1.42 |
| p | / | 0.431 | 0.325 | 0.493 |

the degree of postoperative pain and postoperative anxiety in patients undergoing hysterectomy. Some studies have also found that intravenous injection of hydromorphone hydrochloride can significantly improve anger, anxiety and other emotions, and help to relieve postoperative pain, which is consistent with the results of this study. In addition, the VAS score of the observation group decreased significantly until 12 h after operation, but the duration of intravenous injection of hydromorphone hydrochloride was only 2-3 h. The action time of the same drug was significantly different due to different administration time, which could not be explained by pharmacological mechanism alone^[10]. This phenomenon may be due to the inhibition of central and peripheral pain sensitization by preemptive analgesia with hydromorphone hydrochloride. Thus, the pain threshold of the patients in the observation group can be maintained at a high level without excessive pain response, which is related to prolonging the time of analgesia. Some studies have also shown that postoperative hyperalgesia induced by remifentanyl may be related to the abnormal response of central nervous system tetra receptor, and opioids can significantly inhibit hyperalgesia after remifentanyl anesthesia^[11]. At the same time, this study found that the 6 h VAS score of the two groups was the highest after extubation. It may be related to incision pain and visceral traction pain caused by CO₂ pneumoperitoneum, and the absorption of residual CO₂ in abdominal cavity reached the highest level at 6 h after operation. Cheng Minghua^[12], in the observation of postoperative pain in patients undergoing laparoscopic hysterectomy, it was found that incision pain was the main pain within 12 h after operation, and the peak of pain appeared at 6 h after operation. Aitola^[13] also found that compared with patients who underwent laparoscopic hysterectomy under N₂O and CO₂ pneumoperitoneum, the pain was more severe in CO₂ pneumoperitoneum group 6 h after operation, which supported the results of this study.

This study also found that there was no significant difference in the recovery time of anesthesia and the incidence of nausea, vomiting and respiratory depression between the two groups. The reason may be that the adverse reactions of opioids are mostly

related to the activation of μ -receptors. The affinity of hydromorphone hydrochloride to the receptor is only about half that of morphine, which reduces the incidence of adverse reactions^[14], but the affinity to K-receptor is twice as much as that of morphine. The activation of K-receptor can produce good analgesic effect, but does not cause respiratory inhibition^[15]. A meta-analysis of hydromorphone hydrochloride and morphine showed that compared with morphine, hydromorphone hydrochloride used for postoperative analgesia, the adverse reactions such as nausea, vomiting and skin pruritus were improved, and the incidence of adverse reactions such as respiratory inhibition was lower^[16]. In the study of 80 patients undergoing laparoscopic gynecological surgery, Zhang^[17] also found that intravenous injection of hydromorphone hydrochloride into 15 min before the end of the operation, did not prolong the extubation time and did not increase the incidence of postoperative respiratory depression, which supported the results of this study.

As a source of stress, postoperative pain can stimulate the body to cause a reflex increase in blood pressure and HR. Laparoscopic cholecystectomy has the advantages of less injury and rapid recovery^[18]. However, patients will also have adverse effects on rehabilitation due to increased stress response caused by postoperative pain^[19]. This study found that although the postoperative MAP and HR of the two groups increased, the rising range of the observation group was lower than that of the control group, and the duration was shorter than that of the control group, indicating that preemptive analgesia with hydromorphone hydrochloride in laparoscopic cholecystectomy can better maintain the stability of cardiovascular system after operation. Sinatra^[20] found that preoperative intravenous injection of hydromorphone 0.5 ml can make the perioperative hemodynamics of patients undergoing abdominal surgery more stable and make patients get through the perioperative period well, which is consistent with the results of this study.

Author's contributions:

XinYan Lian and Li GuoLin contributed equally to this work.

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Conflict of interests:

The authors declared no conflict of interest.

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