International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2022.534.542

Research Article
Perioperative Effects of Hydromorphone in Gynecological Laparoscopic Surgery under General Anesthesia

[1]Changhua Ma, [2]Dan Zhao, [1]Xiaolan Hu, [1]Chang Li, [1]Jing Zhang, [1]Yiping Zhang and [1]Linhui Yuan

[1]Department of Anaesthesiology, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi 330006, China
[2]Department of Anaesthesiology, Jiangxi Cancer Hospital, Nanchang, Jiangxi 330029, China

Abstract

Background and Objective: The laparoscopic technique has been widely used in clinical gynaecology because of its advantages on smaller wounds, low perioperative stress responses and fewer postoperative complications. It is necessary to actively examine a drug with accurate effect and high safety to reduce organ damages and promote smooth operation. This study aimed to explore the perioperative effects of hydromorphone on oxidative stress, renal and immune functions and inflammatory factors in gynaecological laparoscopic surgery under general anaesthesia. **Materials and Methods:** Sixty patients who underwent gynaecological laparoscopic surgery under general anaesthesia were selected and divided into 2 groups by random number table method, including a control group (n = 30, treated with the same amount of normal saline) and an observation group (n = 30, pretreated with hydromorphone). **Results:** The observation group had shorter anaesthesia onset time, block time and postoperative recovery time and lower anaesthesia dosage than the control group ($p<0.05$). The observation group had lower serum O_2^-, H_2O_2, OH, MDA content, BUN, UA, Cr content and TNF-α, IL-6 and S-100 β contents at T_1 and T_2 but had higher GSH-Px and SOD content and serum Terg, TGF-β1, IL-10 levels and serum CD3+ and CD4+ levels at T_1 and T_2 than the control group ($p<0.05$). **Conclusion:** Pretreatment with hydromorphone for patients undergoing gynaecological laparoscopic surgery under general anaesthesia can relieve cellular immune suppression induced by surgical stress, improve oxidative stress responses and renal function, reduce the expression of inflammatory factors and relieve the pain degree of patients.

Key words: Gynaecological laparoscopic surgery, general anaesthesia, hydromorphone, oxidative stress, renal function, μ-opioid receptor, ischemia

Citation: Ma, C., D. Zhao, X. Hu, C. Li, J. Zhang, Y. Zhang and L. Yuan, 2022. Perioperative effects of hydromorphone in gynecological laparoscopic surgery under general anesthesia. Int. J. Pharmacol., 18: 534-542.

Corresponding Author: Linhui Yuan, Department of Anesthesiology, The Second Affiliated Hospital of Nanchang University, No.1, Minde Road, East Lake District, Nanchang, Jiangxi 330006, China Tel: +86-0791-86299131

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

In recent years, the laparoscopic technique has been widely used in clinical gynaecology because of its advantages on smaller wounds, low perioperative stress responses and fewer postoperative complications[1]. However, surgery is still an invasive operation. Surgical invasion of the body can activate many inflammatory mediators. Furthermore, the stimulation of different degrees of pain after surgery can also lead to the disorder of the body's inflammatory mechanism. Several proinflammatory factors are released, which causes ischemia-reperfusion injury of the abdominal organs. The patient's liver and kidney functions may temporarily decline reversibly[2]. Therefore, it is necessary to actively examine a drug with accurate effect and high safety to reduce organ damages and promote smooth operation.

Hydromorphone is a semisynthetic derivative of pure μ-opioid receptor agonists and has the advantages of strong efficacy, fast onset, high affinity and few adverse reactions, which is commonly used for cancer pain and chronic pain[3]. Some studies have discovered that the application of hydromorphone during the perioperative period can reduce the conduction of noxious stimulation and reduce the stress response caused by surgery via preventing the sensitization of the central nervous system and peripheral nervous system[4,5]. However, there are few clinical studies on the application of hydromorphone pretreatment to improve the immune function, renal function and inflammatory response in gynaecological patients under general anaesthesia. Designed to provide a scientific reference for the rational administration of clinical anaesthesia programs, this research aimed to explore the perioperative effects of hydromorphone on oxidative stress, renal and immune functions and inflammatory factors in gynaecological laparoscopic surgery under general anaesthesia.

MATERIALS AND METHODS

Study area: The study was carried out in the Department of Gynaecology of The Second Affiliated Hospital of Nanchang University, China from January, 2017-February, 2020.

General information: A total of 60 patients, aged 32-58 years and weighing 44-68 kg, underwent gynaecological laparoscopic surgery under general anaesthesia in the Department of Gynaecology of our hospital from January, 2017-February, 2020 were selected. This study meets the standards set by the medical ethics committee of the second Affiliated Hospital of Nanchang University. All study participants provided written informed consent before participating in the study.

Inclusion and exclusion criteria

Inclusion criteria are as follows:

- Class I or II classified by the American Society of Anesthesiologists (ASA)[6]
- Meeting the relevant standards in the gynecological laparoscopy diagnosis and treatment standard[7]
- Aged 30-60 years old
- No abnormal status in preoperative blood biochemical indicators, Electrocardiogram (ECG), electrolytes and other indicators
- Meeting the indications related to surgery and anaesthesia
- Voluntary signing of the informed consent

Exclusion criteria are as follows:

- Accompanied by inflammatory diseases, immune system diseases, endocrine system diseases, blood diseases, etc
- With important organ (heart, lung, kidney, etc.) dysfunction or failure
- Taking gastric motility drugs, hepatic microsomal enzyme inductor and antacid drugs 1 week before surgery
- Dosed with immunosuppressants, hormones or long-term antidepressant and sedative drugs during perioperative
- Allergic to hydromorphone drugs and switched to open surgery during the operation

Methods

Sample size calculation: Sample size was estimated according to sample size estimation in clinical research edited by Wu and Wang. The sample size estimation method when comparing the 2 sample mean was as follows.

Referring to the formula:

$$n = \left((z\alpha + z\beta) \frac{\sigma}{\delta} \right)^2, \; n = 25$$

was obtained. Considering that unpredictable factors were leading to the drop-out cases, an additional 20% was added, i.e., 30 cases in each group were selected for the study. A total of 60 patients were enrolled in this clinical trial, with 30 patients in each group.

Both groups of patients who underwent gynaecological laparoscopic surgery under general anaesthesia had been administered with intramuscular injection of 0.5 mg atropine (specification, 1 mL:0.5 mg, Zhongfu Pharmaceutical Co., Ltd., National Pharmaceutical Standard H37021060), 0.1 g phenobarbital sodium injection (specification, 1 mL: 0.1 g, Tianjin Jinyao Pharmaceutical Co., Ltd., National Pharmaceutical standard H12020381) 30 min before surgery. Patients' veins were kept open after entering the operating room. The observation group was given hydromorphone pretreatment 15 min before skin cutting, that is, intravenous infusion of 100,000 U hydromorphone (specification, 0 mL: 10 mg, Yichang Humanwell Pharmaceutical Co., Ltd., National Pharmaceutical Standard H20120095). The control group was treated with the same amount of saline solution 15 min before skin cutting. Both groups were rapidly induced intravenously with the sequence of 0.05 mg kg^{-1} midazolam, 0.2 mg kg^{-1} etomidate, 0.2 mg kg^{-1} cisatracurium and 0.5 μg kg^{-1} sufentanil. The tracheal catheter was inserted after 3 min of mask oxygenation, followed by connecting anaesthetic machine to control the breathing. At the same time, the partial pressure end-tidal carbon dioxide ($PetCO_2$) was monitored within 35-45 mm Hg. During the surgery, 4-10 mg/kg/hr propofol and 0.1-0.2 μg/kg/min remifentanil were continuously infused intravenously to maintain the depth of anaesthesia. Bispectral Index (BIS) was used to determine the depth of anaesthesia and adjust the medication, which was maintained within the range of 50±5. Muscle relaxation was maintained with an intermittent injection of 0.1 mg kg^{-1} cisatracurium. The infusion of propofol and remifentanil was stopped 5 min before surgery. The tracheal tube was removed after the patient recovered from spontaneous breathing and was conscious, with a tidal volume of >400 mL, with the blood oxygen saturation of >95% after stopping oxygen inhalation and breathing air for 5 min, with $PetCO_2$ of<5.99 kPa and the swallowing reflex was active.

Indexes observed:

- **Anesthesia effect:** The time spent on anaesthesia onset and block and postoperative recovery of the 2 groups were recorded and the amount of anaesthetic used was noted
- **Laboratory indicators:** The patient's venous blood was taken and centrifuged for 5 min (centrifugal condition, speed, 3000 rpm min^{-1}, radius, 6 cm) at three time points (T_0, before anaesthesia, T_1, 2 hrs since operation initiation, T_2, 24 hrs after operation). Following the removal of the supernatant, the serum level was measured in superoxide anion (O_2^-), Hydrogen Peroxide (H_2O_2), Hydroxyl Radical (OH), Malondialdehyde (MDA), Glutathione Peroxidase (GSH-Px) and Superoxide Dismutase (SOD) content by enzyme-linked immunosorbent assay. The detection kits were purchased from Beijing Northern Biotechnology Research Institute Co., Ltd. Flow cytometry was used to detect CD4+CD25+ regulatory T cells (Treg), intracellular cytokines of IL-10 and Transforming Growth Factor-β1 (TGF-β1), with the testing kits selected from Shanghai Rongbai Biotechnology Co., Ltd. Interleukin-6 (IL-6), Tumour Necrosis Factor-α (TNF-α) and plasma S-100β protein (S-100β) were determined under radioimmunoassay with kits purchased from Shanghai Xinfan Biological Technology Co., Ltd. An automatic biochemical analyzer (manufactured by Hitachi, Japan, model no., 7600) was used to identify the Blood Urea Nitrogen (BUN), Uric Acid (UA) and Muscle Anhydride (Cr) and flow cytometry (manufactured by Beckman Coulter, USA, model no., FC500 MCL) was used to determine T cell subsets, including CD3+, CD4+ and CD8+. All abovementioned operations were strictly performed following the instructions
- **Analgesic effect:** Visual Analogue Scale (VAS) was used to evaluate the pain degree of patients at 1, 2, 4, 8, 12 and 24 hrs after surgery. The scale had a score of 0-10, with 0 as painless and 10 as severe pain and higher scores represented severer pain
- **Complications:** Whether the patients had symptoms, such as lung infection, respiratory depression, cognitive dysfunction, gastrointestinal discomfort (nausea, vomiting, etc.) was observed

The diagnostic criteria for lung infection are:

- Increased sputum, with the special intention of appearance of pus or increased pus
- Oral temperature >38 in >24 hrs
- Occurrence of new invasive changes illustrated by chest X-ray
- Moist rale heard

Statistical analysis: SPSS22.0 software was utilized for data processing. Measurement data were expressed as ($\bar{\chi}\pm S$). Independent sample t-test was used for comparison between groups and paired samples t-test was used for intra-group comparison. Count data were expressed as a percentage. By using the χ^2 test, $p<0.05$ was considered statistically significant.

RESULTS

Baseline data: The baseline data of the 2 groups in terms of gender, age, Body Mass Index (BMI), operation time, ASA classification and operation type were well balanced ($p>0.05$) and comparable (Table 1).

Anaesthesia effect: Compared with the control group, the observation group had a shorter anaesthesia onset time (Fig. 1a), lesser anaesthesia medication (Fig. 1b), shorter block time (Fig. 1c) and postoperative recovery time (Fig. 1d) ($p<0.05$). It is suggested that hydromorphone can significantly enhance the effects of anaesthesia on patients undergoing gynaecological laparoscopic surgery under general anaesthesia.

Oxidative stress indicators: The oxidative stress indicators of the observation group at T_1 were not statistically different from those of the control group ($p>0.05$). Moreover, serum O_2^- (Fig. 2a), H_2O_2 (Fig. 2b) and OH (Fig. 2c) and the MDA (Fig. 2d) content of the observation group at T_1 and T_2 were lower but GSH-Px (Fig. 2e) and SOD (Fig. 2f) content were higher compared to those of the control group ($p<0.05$).

Renal function: There was no significant difference in terms of renal function indicators at T_1 between the two groups ($p>0.05$). The serum BUN (Fig. 3a), UA (Fig. 3b) and Cr (Fig. 3c) content of the observation group at T_1 and T_2 were lower compared with the control group ($p<0.05$). It is indicated that pretreatment with hydromorphone during gynaecological laparoscopic surgery under general anaesthesia can significantly improve the renal function of patients.

Inflammatory factors: There was no significant difference in the indicators of inflammatory factors at T_1 between the two groups ($p>0.05$). Furthermore, the serum TNF-α (Fig. 4a), IL-6 (Fig. 4b) and S-100β (Fig. 4c) content of the observation group

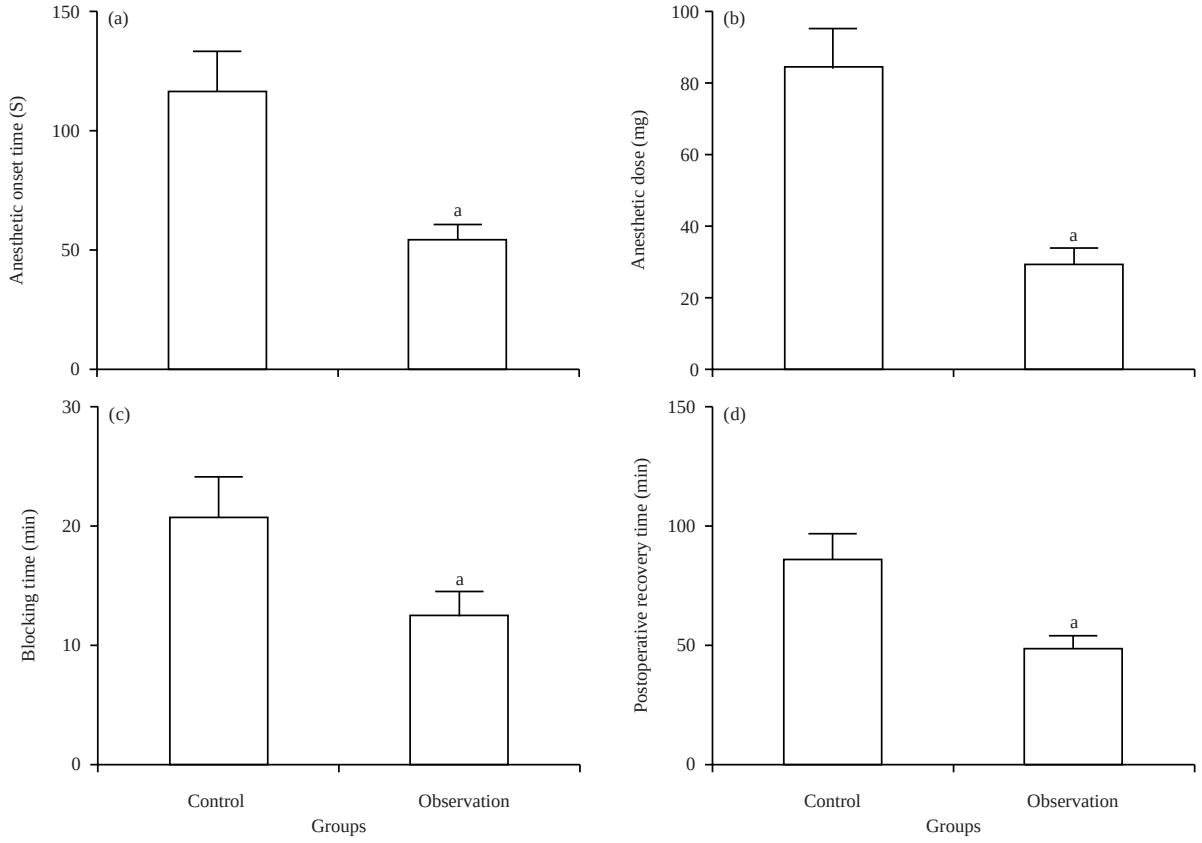

Fig. 1(a-d): Effect of hydromorphone on anaesthesia effect of patients, in patients administrated with Hydromorphone, (a) Onset time of anaesthesia, (b) Dosage of anaesthesia was lower than the control group, (c) Blocking time and (d) Postoperative recovery time were significantly shorter than the control group and
Compared with the control group and $^a p<0.05$

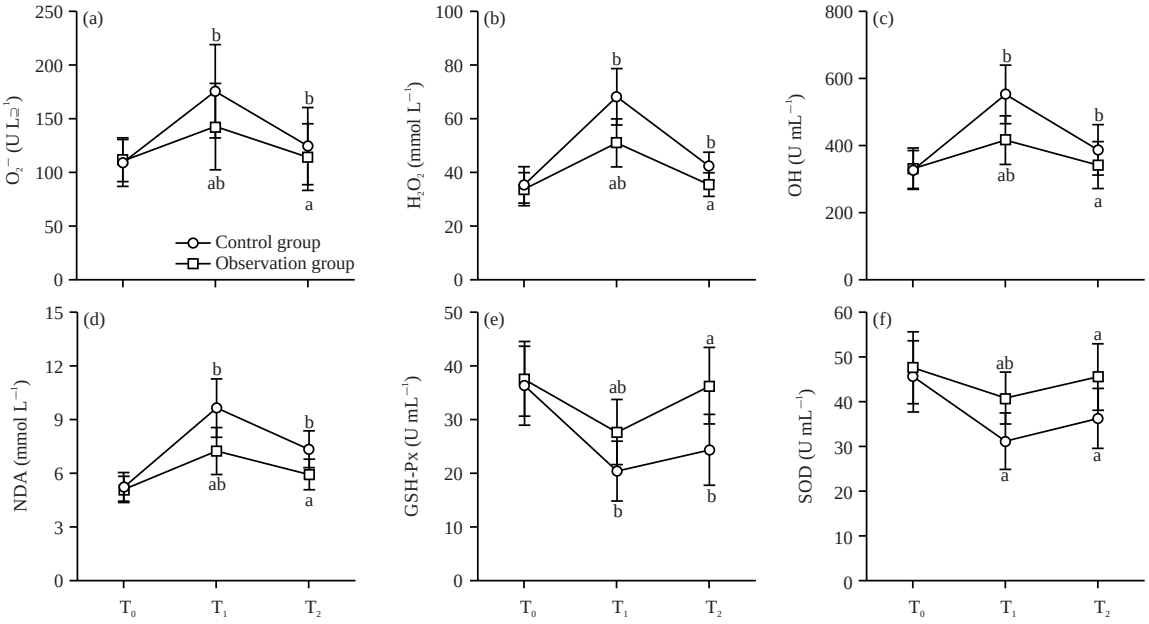

Fig. 2(a-f): Effect of hydromorphone on oxidative stress indicators in patients, in patients administrated with hydromorphone, the levels of (a) O_2^-, (b) H_2O_2, (c) OH and (d) MDA were lower than those in the control group at T_1 and T_2, the content of (e) GSH-Px and (f) SOD were higher than those in the control group

Compared with the control group during the same period, [a]p<0.05, compared within the group at T_0 and [b]p<0.05

Table 1: Comparison of baseline data

Groups	Age (years)	BMI (kg m^{-2})	Time of operation (min)	ASA rating		Operation type		
				Class I	Class II	Hysteromyomectomy	Ovarian cystectomy	Total hysterectomy
Control (n = 30)	40.37±5.27	23.15±2.98	96.74±6.89	17	13	6	15	9
Observation (n = 30)	41.74±6.09	23.97±3.01	94.48±7.15	16	14	8	16	6

at T_1 and T_2 were lower in comparison to the control group (p<0.05). It is suggested that hydromorphone pretreatment in gynaecological laparoscopic surgery under general anaesthesia can reduce the inflammatory response rate of patients.

Cellular immune factors: There was no statistically significant difference in terms of indicators of cellular immune factors at T_1 between the two groups (p>0.05). The serum terg (Fig. 5a), IL-10 (Fig. 5b) and TGF-β1 (Fig. 5c) levels at T_1 and T_2 in the observation group were higher compared to the control group (p<0.05). It is suggested that pretreatment with hydromorphone during gynaecological laparoscopic surgery under general anaesthesia can significantly improve cellular immune factor levels of patients.

Changes of T lymphocyte subsets: Concerning the comparison of T lymphocytes indicators at T_1 between the observation and control groups, the difference was not statistically significant (p>0.05). The serum CD3+ (Fig. 6a) and CD4+ (Fig. 6b) levels in the observation group at T_1 and T_2 were higher than those in the control group (p<0.05). In terms of serum CD8+ (Fig. 6c) levels at T_1 and T_2 between the two groups, there was no statistical significance (p>0.05). It is suggested that pretreatment with hydromorphone in gynaecological laparoscopic surgery under general anaesthesia can significantly improve the immune function of patients.

VAS scores: The VAS scores of the observation group at 1, 2 and 4 hrs after surgery were lower than those of the control group (p<0.05). It was suggested that pretreatment with hydromorphone can significantly reduce the postoperative pain degree of patients undergoing gynaecological laparoscopic surgery under general anaesthesia with the rapid and obvious analgesic effect as illustrated in Table 2.

Complications: In the comparison of the incidence of complications between the observation group (10.00%) and

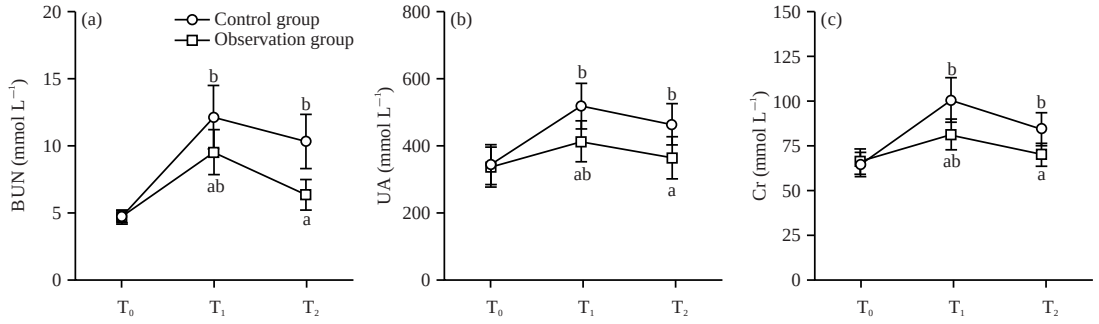

Fig. 3(a-c): Effect of hydromorphone on renal function indicators in patients, in patients administrated with hydromorphone, the serum levels of (a) BUN, (b) UA and (c) Cr at T_1 and T_2 were lower than those in the control group

Compared with the control group during the same period, [a]p<0.05, compared within the group at T_0 and [b]p<0.05

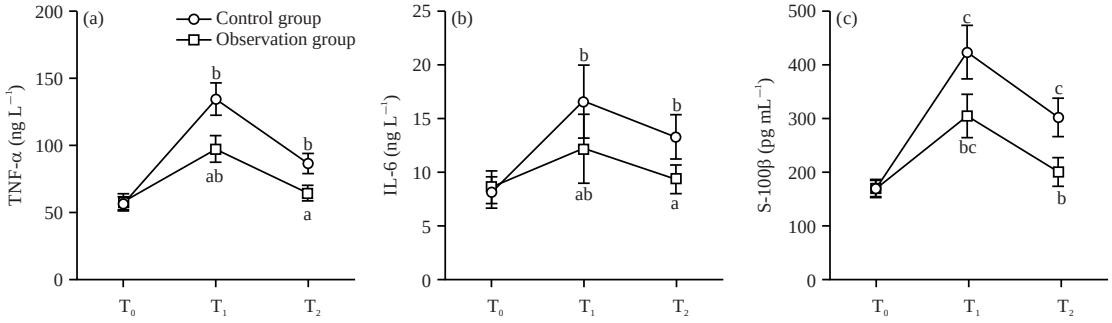

Fig. 4(a-c): Effect of hydromorphone on inflammatory cytokines in patients, in patients administrated with hydromorphone, the serum levels of (a) TNF-α, (b) IL-6 and (c) S-100β were lower than those in the control group

Compared with the control group during the same period, [a]p<0.05, compared within the group at T_0 and [b]p<0.05

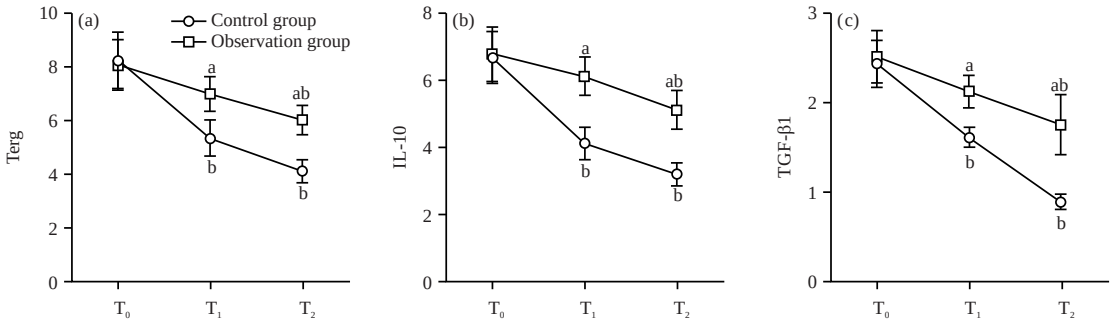

Fig. 5(a-c): Effect of hydromorphone on cellular immune factors in patients, in patients administrated with hydromorphone, the serum levels of (a) Terg, (b) IL-10 and (c) TGF-β1 at T_1 and T_2 were higher than those in the control group

Compared with the control group during the same period, [a]p<0.05, compared within the group at T_0 and [b]p<0.05

Table 2: Comparison of VAS scores ($\bar{\chi}\pm S$)

Groups	1 hrs	2 hrs	4 hrs	8 hrs	16 hrs	24 hrs
Control (n = 30)	2.36±0.42	2.41±0.46	2.23±0.38	2.46±0.51	2.71±0.38	2.81±0.46
Observation (n = 30)	1.52±0.63[b]	1.76±0.37[b]	1.82±0.27[b]	2.39±0.55	2.69±0.42	2.72±0.43

Compared with the control group, [b]p<0.05

the control group (6.67%), the difference was not statistically significant (p>0.05). It was suggested that pretreatment with hydromorphone during gynaecological laparoscopic surgery under general anaesthesia would not increase the complication incidence of patients (Table 3).

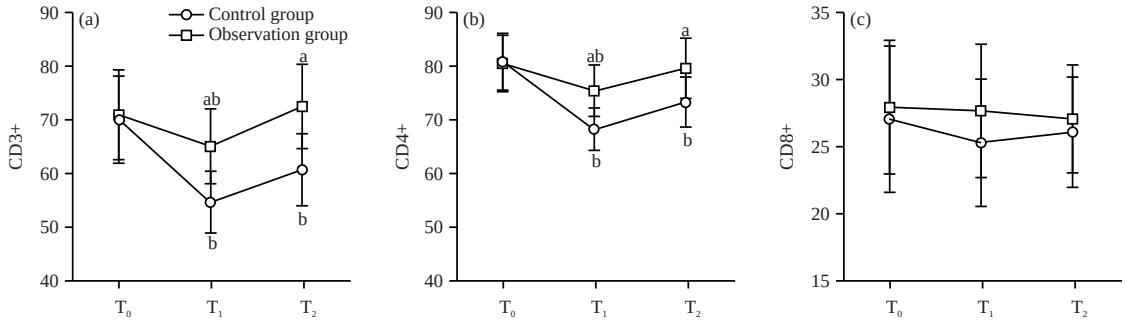

Fig. 6(a-c): Effect of hydromorphone on T lymphocyte changes in patients, in patients administrated with hydromorphone, (a) CD3+, (b) CD4+ and (c) CD8+ were higher than those in the control group

[a]p<0.05, compared within the group at T_0 and [b]p<0.05

Table 3: Comparison of the incidence of complications, n (%)

Groups	Lung infection	Respiratory depression	Gastrointestinal discomfort	Total
Control group (n = 30)	1 (3.33)	0	1 (3.33)	2 (6.67)
Observation group (n = 30)	0	2 (6.67)	1 (3.33)	3 (10.00)
X^2				0.001
P				0.698

DISCUSSION

As a source of traumatic stress, gynaecological laparoscopic surgery can induce different degrees of oxidative stress responses, with main manifestations of antioxidant defence-oxidation mechanism imbalance and hypothalamic-pituitary-adrenal cortical activity promotion. Several inflammation mediators and stress hormones are secreted and accumulated in the tissues, which can lead to lipid peroxidation damages in important tissues and organs and induce vasospasm and contraction, inflammatory reaction and endothelial vascular injury[8,9].

In this study, the serum O_2^-, H_2O_2, OH and MDA content of the observation group at T_1 and T_2 were lower but GSH-Px and SOD content were higher than those of the control group, which was consistent with the study of Gajarawala *et al.*[10]. This further shows that hydromorphone can reduce the stress response of patients under general anaesthesia. The reason may be that hydromorphone can reduce inflammatory cell infiltration, inhibit oxidative stress and reduce the production of oxygen free radicals, at the same time, pretreatment of hydromorphone can inhibit central and peripheral sensitization, prevent noxious stimulation through μ-receptor and κ-receptor activation and then reduce the release of NE and E, inhibit bradykinin-mediated nociceptive sensitization and alleviate stress response[11]. In addition, this study found that hydromorphone pretreatment can help reduce renal tubular dysfunction and decrease renal blood flow caused by general anaesthesia and prevent renal impairment. The reason may be related to the fact that hydromorphone can improve portal blood flow, prevent the decrease of renal blood flow, avoid the aggravation of renal injury and then play a role in protecting renal tubular function[12].

The CO_2 artificial pneumoperitoneum during the operation will increase the pressure in the abdominal cavity to a certain extent and change the blood supply of the abdominal viscera and abdominal wall tissue, resulting in poor perfusion of the abdominal viscera and tissues and release of numerous inflammatory factors. After the pneumoperitoneum is removed, ischemia-reperfusion injury exacerbates systemic inflammation[11]. IL-6 is one of the inflammatory mediators, which can more sensitively reflect the level of the body's stress responses. Abnormally increased IL-6 content can trigger the release of other inflammatory factors, such as TNF-α. S-100β protein is a brain-specific protein with a half-life period of about 2 hrs in the body. As one of the main markers of brain injury, it participates in several activities of glial cells in the central nervous system, such as growth, differentiation, proliferation and maintenance of calcium homeostasis[13]. Related studies have found that the higher the serum S-100β content is, the greater brain damages there are in the patients. Furthermore, the protein content can be used as an index to predict the risk of Postoperative Cognitive Dysfunction (POCD)[14]. In this study, the serum TNF-α, IL-6, S-100β content of the observation group at T_1 and T_2 and the VAS scores of the observation group at 1, 2 and 4 hrs after surgery were lower compared to those of the control group, which demonstrates that hydromorphone pretreatment can exert an analgesic

effect, reduce the release and production of proinflammatory cytokines during pneumoperitoneum and lower inflammation. The main reasons are related to the following mechanisms of hydromorphone: (1) Hydromorphone can avoid the production of a large number of oxygen free radicals during stress, reduce the release of stress-related cytokines and reduce the release of IL-6, IL-8 and other cytokines, thereby preventing the excessive inflammatory response of the body after surgery, (2) Hydromorphone can play an effective analgesic effect, prevent the transfer of noxious stimulation to the central nervous system caused by surgical incision and inflammatory reaction, prevent the allergic reaction of the central nervous system and then reduce the inflammatory response induced by noxious stimulation[15,16].

Clinical studies have found that T cell-mediated cellular immunity plays a significant role in tumorigenesis, disease progression and prognosis[17,18]. When the levels of CD3+, CD4+ and CD8+ are disturbed, the body is in an immunosuppressive state and a lot of tumour cells can escape the surveillance of immune cells, which may induce infection or cause aggravation of the disease[19,20]. Coaccioli *et al.*[21] found that hydromorphone had no obvious effects on immunoglobulin, cellular immunity, complement components, T lymphocyte subsets and other immune parameters and had no inhibition on immune capacity and immune response. There are varying degrees of reduction in immune cytokines in the two groups after the anaesthesia in the study. However, serum levels of Terg, TGF-β1, IL-10, CD3+ and CD4+ in the observation group at T_1 and T_2 were higher than those in the control group, which illustrates that hydromorphone can effectively prevent the decrease of Terg and its factors, regulate the activity of Terg, suppress the stress state and improve the immune function, which is slightly different from the above research results. Therefore, it is necessary to expand the sample size and further explore the mechanism of action of hydromorphone in the later stage to confirm the conclusion of this study. In addition, this study found that hydromorphone has certain advantages in shortening the onset time of the anaesthesia effect, improving the anaesthesia effect and reducing the dosage of anaesthesia. The possible reason is related to the shorter onset time, half-life and blood-brain barrier elimination time of hydromorphone, which makes it easier to pass through the blood-brain barrier and then act on the central nervous system rapidly[10]. From the perspective of safety, in this study, there was no significant difference in the incidence of complications between the observation group and the control group, indicating that hydromorphone pretreatment did not increase the occurrence of complications and the safety was relatively high.

CONCLUSION

In summary, pretreatment with hydromorphone for patients undergoing gynaecological laparoscopic surgery under general anaesthesia can relieve cellular immune suppression induced by surgical stress, improve oxidative stress responses and renal function, reduce the expression of inflammatory factors and reduce the pain degree of patients, with high safety. However, there are certain limitations to this study, such as the small sample size and few observation time points. In the future, large sample sizes, multicenter and prospective researches are warranted.

SIGNIFICANCE STATEMENT

This study discovers that pretreatment with hydromorphone for patients undergoing gynaecological laparoscopic surgery under general anaesthesia can significantly relieve cellular immune suppression induced by surgical stress, improve oxidative stress responses and renal function, reduce the expression of inflammatory factors and reduce the pain degree of patients, which is beneficial to the tolerance of surgery and promote the recovery of patients. This study will help researchers to uncover the critical areas where hydromorphone can reduce surgical stress in patients undergoing gynaecological laparoscopic surgery that other researchers were not able to explore. Thus, a new theory may arrive at that hydromorphone can effectively help gynaecological patients to complete the surgery successfully.

REFERENCES

1. Jung, H.J., J.Y. Park, D.Y. Kim, D.S. Suh and J.H. Kim *et al.*, 2018. Comparison of laparoscopic and open surgery for patients with borderline ovarian tumors. Int. J. Gynecologic Cancer, 28: 1657-1663.
2. Asadollah, S., M. Vahdat, P. Yazdkhasti and N. Nikravan, 2014. The influence of dexamethasone on postoperative nausea and vomiting in patients undergoing gynecologic laparoscopic surgeries: A randomised, controlled, double blind trial. J. Turk. Soc. Obstetric Gynecol., 11: 219-223.
3. Mazer-Amirshahi, M., S. Motov and L.S. Nelson, 2018. Hydromorphone use for acute pain: Misconceptions, controversies and risks. J. Opioid Manage., 14: 61-71.
4. Bao, Y.J., W. Hou, X.Y. Kong, L. Yang, K. Jones, J. Xia and B.J. Hua, 2014. Hydromorphone for cancer pain. Cochrane Database Syst. Rev., Vol. 10. 10.1002/14651858.cd011108.
5. Sharpe, E.E., R.J. Molitor, K.W. Arendt, V.E. Torbenson and D.A. Olsen *et al.*, 2020. Intrathecal morphine versus intrathecal hydromorphone for analgesia after cesarean delivery. Anesthesiology, 132: 1382-1391.

6. Mupparapu, M. and S.R. Singer, 2018. Editorial: The american society of anesthesiologists (ASA) physical status classification system and its utilization for dental patient evaluation. Quintessence Int., 49: 255-256.
7. Bentskivs'kyĭ, B.M., V.G. Zhegulovych, I.Ĭ. Kryzhanovs'kyĭ, M.M. Stets, R.O. Mel'nyk and V.M. Chernenko, 2012. Differential approach to the diagnosis of acute appendicitis and acute gynecological pathology in pregnant women. Lik Sprava, 1-2: 107-112.
8. Landolf, K.M., R.M. Rivosecchi, H. Goméz, C.M. Sciortino and H.N. Murray *et al*., 2020. Comparison of hydromorphone versus fentanyl based sedation in extracorporeal membrane oxygenation: A propensity matched analysis. Pharmacotherapy, 40: 389-397.
9. Reddy, A., M. Vidal, S. Stephen, K. Baumgartner and S. Dost *et al*., 2017. The conversion ratio from intravenous hydromorphone to oral opioids in cancer patients. J. Pain Symptom Manage., 54: 280-288.
10. Gajarawala, S., A. Wells, E. Watkins, B. Rust and M. Archambault, 2020. Intrathecal hydromorphone as an analgesia option for gynecology patients. J. Am. Acad. Physician Assistants, 33: 33-37.
11. Sato, N., E. Satomi, T. Yoshida, M. Shimizu, D. Kiuchi and H. Ishiki, 2020. Hydromorphone in cancer patients-A retrospective study. Gan To Kagaku Ryoho., 47: 1687-1690.
12. Sao, C.H., M. Chan-Tiopianco, K.C. Chung, Y.J. Chen, H.C. Horng, W.L. Lee and P.H. Wang, 2019. Pain after laparoscopic surgery: Focus on shoulder-tip pain after gynecological laparoscopic surgery. J. Chin. Med. Assoc., 82: 819-826.
13. Balyan, R., M. Dong, V. Pilipenko, K. Geisler, A.A. Vinks and V. Chidambaran, 2020. Hydromorphone population pharmacokinetics in pediatric surgical patients. Pediatr. Anesthesia, 30: 1091-1101.
14. Nystrom, M.R., A. Odunayo and C.C. Okafor, 2019. Assessment of hydromorphone and dexmedetomidine for emesis induction in cats. J. Vet. Emergency Crit. Care, 29: 360-365.
15. Chinn, E., B.W. Friedman, F. Naeem, E. Irizarry and F. Afrifa *et al*., 2019. Randomized trial of intravenous lidocaine versus hydromorphone for acute abdominal pain in the emergency department. Ann. Emergency Med., 74: 233-240.
16. Ma, K., Y. Jin, L. Wang, Z.Y. Feng and T. Song *et al*., 2020. Intrathecal delivery of hydromorphone vs morphine for refractory cancer pain: A multicenter, randomized, single-blind, controlled noninferiority trial. Pain, 161: 2502-2510.
17. Reed, R.A., H.K. Knych, M. Barletta, D.M. Sakai, M.M. Ruch, C.A. Smyth and C.A. Ryan, 2020. Pharmacokinetics and pharmacodynamics of hydromorphone after intravenous and intramuscular administration in horses. Vet. Anaesth. Analg., 47: 210-218.
18. Kovacevic, M.P., P.M. Szumita, K.M. Dube and J.R. DeGrado, 2020. Transition from continuous infusion fentanyl to hydromorphone in critically Ill patients. J. Pharm. Pract., 33: 129-135.
19. Mazereeuw, G., T. Gomes, E.M. Macdonald, S. Greaves and P. Li *et al*., 2020. Oxycodone, hydromorphone and the risk of suicide: A retrospective population-based case-control study. Drug Saf., 43: 737-743.
20. Rodrigues, S., D. Shin, M. Conway, S. Smulski and E. Trenker *et al*., 2021. Hydromorphone versus morphine: A historical cohort study to evaluate the quality of postoperative analgesia. Can. J. Anesthesia/J. Canadien d'Anesthésie, 68: 226-234.
21. di Coaccioli, S., L. Di Cato, A. Panaccione, M.E. Crapa, A. Paladini, A. Piroli and F. Marinangeli, 2013. Hydromorphone does not influence the immune response in patients affected by chronic pain. Clin. Terapeutica, 164: 97-99.