The Efficacy and Safety of Nabufen and Sufentanil in the Prevention of Visceral Pain After Gynecological Laparoscopic Surgery: A Randomised Controlled Trial

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Research article

Keywords: nalbuphine, sufentanil, visceral pain after laparoscopic surgery, optimal compatibility

Posted Date: December 14th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-125287/v1

Abstract

Background: To compare the efficacy and safety of different compatibility schemes in the prevention of visceral pain after gynecological laparoscopic surgery.

Methods: from April 2019 to April 2020, patients undergoing elective gynecological laparoscopic surgery in our hospital were randomly divided into four groups: group A: sufentanil 3 μ g / kg; group B: low-dose nalbuphine group: 0.1 mg / kg of nabufen + 3 μ g / kg of sufentanil; group C: medium dose of nabufen group: 1 mg / kg of nabufen + 2 μ g / kg of sufentanil; group D: high-dose nabufen 2 There were 30 cases in each group. The degree of pain and the number of adverse reactions at 2, 4, 8, 12, 24 and 48 hours after operation were observed and recorded. The number and dosage of morphine used as a remedial analgesic were recorded. The pain degree was assessed by visual analogue scale (VAS). The total amount of analgesic pump used, the total number of times of pressing and the effective times of pressing were recorded. The adverse reactions included respiratory depression, nausea and vomiting, drowsiness, restlessness and skin The skin itches.

Results: the analgesic effect of group B was similar to that of group A, and there was no significant difference in the number of invalid pressing, total pressing times and rescue analgesia rate ($P > 0.05$), while the invalid pressing times, total pressing times and remedial analgesia rate of group C and group D were significantly lower than those of group A ($P < 0.05$). There was no significant difference between group C and group D in the number of invalid compressions, the total number of compressions and the rate of remedial analgesia ($P > 0.05$), suggesting that increasing the dose of nalbuphine could not significantly increase the analgesic effect. The incidence of postoperative nausea and vomiting, skin pruritus, lethargy and Ramsay Sedation score in group B and group C were significantly lower than those in group A ($P < 0.05$). Ramsay Sedation score and incidence of drowsiness were lower than those in group D, which indicated that the incidence of adverse reactions was higher in group D than group B and group C.

Conclusion: the combination of 1 mg / kg nabufen and 2 μ g / kg sufentanil is a safe and effective combination scheme for the prevention of visceral pain after gynecological laparoscopic surgery with small adverse reactions.

Trial registration: http://www.chictr.org.cn/showproj.aspx?proj=40635

Registration number□ChiCTR1900025076 . Prospectively registered on 10 August 2019.

Background

Because of the small incision and small trauma of laparoscopic surgery, postoperative analgesia is generally insufficient, and postoperative nausea and vomiting are more likely. Many of them reach moderate or severe pain. The nature of the pain is mainly visceral pain, and the pain is more severe than the surgical wound. These are often ignored and need our attention urgently. Therefore, effective

postoperative analgesia is particularly important. Nabuphin is an opioid receptor agonist antagonist, which can completely activate the κ receptor, has a rapid onset, and has a significant inhibitory effect on visceral pain [1]; it has a partial antagonistic effect on μ receptor, and has a low incidence of adverse reactions such as nausea, vomiting and skin pruritus when used for postoperative analgesia [2, 3] Therefore, in this study, patient - controlled intravenous analgesia (PCIA) was used to optimize and screen the best combination of nabufen and sufentanil to prevent visceral pain after gynecological laparoscopic surgery, and strive to achieve the balance between the maximum analgesic effect and the minimum adverse reactions, so as to achieve the ultimate goal of high patient satisfaction and low economic burden.

Methods

1.1 General information

Methods from April 2019 to April 2020, 90 patients undergoing laparoscopic hysterectomy in the Affiliated Hospital of Guangdong Medical University were selected as the observation objects. Group A and group C were randomly divided into two groups. All patients had no serious heart, lung, liver, kidney dysfunction and other contraindications, mental state was good, no abnormal fasting blood glucose or postprandial blood glucose was found before operation, and all patients and their families were informed and agreed. There were no significant differences in age, gender, weight and height among the three groups (all P > 0.05), which were comparable, as shown in Table 1.

Table 1
comparison of general conditions of the four groups ($\bar{x} \pm s$)

Group	A(n = 30)	B(n = 30)	C(n = 30)	D(n = 30)	χ^2/F	P
Age (years)	37.6 ± 7.1	38.3 ± 8.4	38.1 ± 5.3	37.9 ± 5.3	1.032	0.512
Height(cm)	157 ± 5.0	156 ± 3.1	155 ± 2.8	156 ± 3.1	0.758	0.465
Weight(kg)	54.7 ± 5.4	54.3 ± 6.1	55.2 ± 3.1	54.5 ± 3.2	0.379	0.813
ASA(□/□)	21/9	22/8	20/10	21/9	0.486	0.412
Operation time(h)	1.21 ± 0.35	1.17 ± 0.41	1.19 ± 0.47	1.21 ± 0.47	0.908	0.921
blood loss(ml)	19.06 ± 6.29	19.47 ± 6.78	20.07 ± 5.32	19.17 ± 6.32	0.584	0.368
Liquid volume(ml)	999.11 ± 113.90	1002.63 ± 107.65	1002.83 ± 108.52	1102.63 ± 111.24	0.865	0.715
Urine output(ml)	188.33 ± 45.26	198.55 ± 53.53	179.85 ± 41.23	179.85 ± 40.53	0.155	0.202
Note:These differences were not statistically significant,*P* > 0.05.						

1.2 Anesthesia method

All patients did not use any preoperative medication. They were fasting for 4-6 hours before operation. After entering the room, nasal catheter continued to inhale oxygen for 3 L / min. ECG, BP, HR, SpO2 were detected, peripheral vein and infusion were opened, and rescue equipment and drugs such as tracheal intubation were prepared. Intravenous infusion of lactate Ringer's solution 8-10 ml / kg was performed by a fixed skilled anesthesiologist. After 3 min of nitrogen and oxygen removal, induction was started. Midazolam 0.03 mg / kg, etomidate 0.3 mg / kg, atracurium CIS besylate 0.2 mg / kg, sufentanil 0.5 UG / kg, At the same time, the fresh oxygen flow rate of mask inhalation was set to 3L / min. after the patient's consciousness disappeared, the laryngoscope was used to intubate through the mouth under the light vision. The endotracheal tube should be "id = 7.0", the surface should be fully lubricated, and the intubation should be successful at one time. After intubation, mechanical ventilation should be set: VT 8ml · kg-1, rr12 times / min. Anesthesia was maintained with propofol 4-6mg / kg / h, atracurium CIS benzenesulfonate 0.2-0.3mg/kg/h, sufentanil 0.2-0.4ug/kg/h, BIS value was controlled between 40-60, PetCO2 was maintained at 35-45mmhg, CO2 pneumoperitoneum pressure was automatically controlled at 12mmhg, sufentanil and cisatracurium sulfonate were stopped 30 minutes before the end of operation, and propofol was stopped 5 minutes before the end of operation.

Laparoscopic surgery was performed in all four groups, and the operation was performed by the same group of doctors. There was no significant difference in operation site, operation time, intraoperative blood loss, intraoperative fluid infusion volume and operation method ($P > 0.05$), which was comparable, as shown in Table 1. After operation, they were randomly divided into four groups: group A: sufentanil 3 μ g / kg; group B: low-dose nalbuphine group: 0.1 mg / kg + 3 μ g / kg sufentanil group; group C: medium dose of nabufen group: 1 mg / kg of nabufen + 2 μ g / kg of sufentanil; group D: large dose of nabufen group: 2 mg / kg of nabufen + 1 μ g / kg of sufentanil; 30 cases in each group. In addition to different intervention measures, the perioperative nursing care of the four groups were the same and were performed according to the conventional methods.

1.3 Observation indicators

The postoperative 48 hours were recorded The highest Ramsay Sedation score within H (restlessness: 1 point; awake, quiet cooperation: 2 points; drowsiness, quick response to instructions: 3 points; light sleep, wake-up: 4 points; sleep, slow response to call: 5 points; deep sleep, call should not be 6 points); rescue analgesia, PCIA invalid pressing times and total pressing times, postoperative nausea and vomiting, skin itching, drowsiness were recorded Situation.

Visual analogue scale (VAS) was used to measure the patient's analgesia. A 10 cm horizontal line was drawn on a piece of paper. The range was 0-10. 0 indicated no pain, 10 was the strongest pain. The closer to 10, the more painful the subjective feeling was. Ask the patient to make a mark on the horizontal line

according to the self feeling on the paper, and then measure the distance from the starting point with a ruler, which is the score value.

1.4 Statistical methods

SPSS18.0 software was used for analysis. The measurement data were expressed as mean ± standard deviation (). The one-way ANOVA, Q-test and t-test were used. Chi square test was used for counting data. The difference was statistically significant with $P < 0.05$.

Results

2.1 comparison of general data

There were no significant differences in age, sex ratio, body weight, ASA grade, operation time, intraoperative bleeding, intraoperative fluid infusion and intraoperative urine volume in 120 patients ($P > 0.05$). See Table 1 for details.

2.2 postoperative analgesia score and use of analgesia pump in four groups (Table 2 and table 3)

Compared with the same group 2 hours after operation, VAS scores of four groups were significantly increased from 8 hours after operation ($P < 0.05$); compared with group A at the same time point, VAS scores of group B were not significantly different ($P > 0.05$); VAS scores of groups C and D were significantly decreased ($P < 0.05$). See Table 2.

Table 2
Comparison of postoperative pain score (VAS) in four groups (n = 30, $\bar{x} \pm s$)

Group	2 h	4 h	8 h	12 h	24 h
A(n = 30)	0.17 ± 0.28	0.39 ± 0.88	0.57 ± 0.99*	0.85 ± 0.92*	1.05 ± 0.52*
B(n = 30)	0.15 ± 0.26	0.35 ± 0.69	0.49 ± 0.97*	0.85 ± 0.67*	0.98 ± 0.64*
C(n = 30)	0.05 ± 0.28#	0.17 ± 0.36#	0.24 ± 0.52*#	0.57 ± 0.65*#	0.65 ± 0.81*#
D(n = 30)	0.05 ± 0.31#	0.19 ± 0.48#	0.29 ± 0.72*#	0.59 ± 0.85*#	0.65 ± 0.72*#
P	0.438	0.053	0.0413	0.034	0.038

Note: Compared with the postoperative 2 h in the same group,*$P < 0.05$;Compared with group A at the same time#$P < 0.05$.

There was no significant difference in the dosage of analgesic pump among the four groups ($P > 0.05$); there was no significant difference in the effective pressing times and total pressing times between group

B and group A (P > 0.05); but it was significantly lower in group C and group D (P < 0.05). Two patients in group a need additional flurbiprofen axetil for analgesia in group B, as shown in Table 3.

Table 3
Use of analgesic pump in four groups (n = 30, $\bar{x} \pm s$)

Group	Dosage of analgesic pump(ml)	Effective press times(□)	Total press times (Times)	Add analgesic (person)
A(n = 30)	92.42 ± 7.77	1.34 ± 0.58#	3.65 ± 1.55#	2
B(n = 30)	93.27 ± 7.06	1.47 ± 0.82#	3.49 ± 0.91#	1
C(n = 30)	94.58 ± 8.16	0.61 ± 0.33*	0.99 ± 0.53*	0
D(n = 30)	93.65 ± 8.11	0.53 ± 0.41*	0.87 ± 0.71*	0
Note: Compared with group A,*$P < 0.05$Compared with group C,#$P < 0.05$				

2.3 comparison of adverse reactions in four groups

There were no respiratory depression adverse reactions in the four groups. There was no significant difference in the incidence of postoperative adverse reactions between group B and group A (P > 0.05), while the incidence of postoperative adverse reactions in group C and group D was significantly lower (P < 0.05), especially in group C. There was also significant difference between group D and group C (P < 0.05). The total incidence of adverse reactions in group C was the lowest, as shown in Table 4.

Table 4
Comparison of postoperative adverse reactions among four groups [cases (%)]

Group	Respiratory depression	Nausea and vomiting	Drowsiness	dizzy	skin Itch	Total
A(n = 30)	0(0%)	15(50.00%)#	5(16.67%)#	6(20.00%)#	2(6.67%)	28(93.33%)#
B(n = 30)	0(0%)	12(40.00%)#	3(10.00%)	5(16.67%)#	0(0%)	20(66.67%)#
C(n = 30)	0(0%)	2(6.67%)*	1(3.33%)*	1(3.33%)*	0(0%)	4(13.33%)*
D(n = 30)	0(0%)	5(16.67%)*#	4(13.33%)#	4(13.33%)#	0(0%)	9(30.00%)*#
Note: Compared with group A,*$P < 0.05$Compared with group C,#$P < 0.05$						

Discussion

Compared with laparotomy, laparoscopic surgery is more suitable for less trauma and less complications. However, laparoscopic surgery is more prone to nausea and vomiting, postoperative pain still exists, many of them reach moderate pain, even severe pain. The nature of pain is mainly visceral pain, and even the pain is more severe than the surgical wound. Visceral pain is different from perceived physical pain. Patients may not feel well-defined pain, but produce a subjective abdominal discomfort that is difficult to say. However, such subjective abdominal discomfort can lead to anxiety, irritability, sweating and other negative emotions accompanied by nausea and vomiting, and even affect cardiovascular and respiratory functions [4]. Therefore, more and more attention should be paid to visceral pain after laparoscopic surgery.

Lovatisis et al. [5] reported that the incidence of severe pain after laparoscopic surgery can reach 10%. Poor postoperative pain control will affect the subjective experience and comfort of patients, thus prolonging the length of hospital stay, delaying postoperative rehabilitation, which is not conducive to the development of enhanced recovery after surgery (ERAS). Moreover, if the postoperative pain is not given adequate treatment, it may become a persistent chronic pain which is often ignored [6].

Patient controlled intravenous analgesia (PCIA) is easy to operate, and patients can add analgesic drugs according to their pain or not. It is safe and widely used in postoperative analgesia.

In 2017, the expert consensus on adult postoperative pain management proposed at the anesthesiology branch of Chinese Medical Association pointed out that strong opioids, namely narcotic analgesics, are the most commonly used drugs for the treatment of moderate to severe acute pain [8]. Opioid drugs are the most commonly used and effective postoperative analgesia, which mainly play the role of three types of receptors: μ, κ, δ [9, 10]. Although all three receptors have analgesic effect, the analgesic mechanism and analgesic effect are not the same due to the different distribution of receptors and different types of receptors. Activation of μ receptor mainly mediates analgesia above spinal cord, κ receptor mainly mediates analgesia and sedation at spinal level, δ receptor mainly couples with μ receptor in structure and regulates μ receptor in function The role of receptors [10, 11].

In fact, PCIA using opioids is indeed the most commonly used postoperative analgesia mode in clinical practice [12]. Sufentanil is commonly used in postoperative PCIA due to its very strong analgesic effect, which belongs to the central μ receptor agonist. It has satisfactory therapeutic effect on the body, but has limited effect on visceral pain [13]. However, its adverse reactions such as nausea and vomiting, respiratory depression, pruritus, tolerance and dependence are obvious, which limit the use of sufentanil to a certain extent. As an opioid receptor agonist antagonist, nabuprofen is also commonly used in postoperative PCIA, but its analgesic effect is weaker than sufentanil. However, in visceral pain model, κ - receptor agonist is the most effective opioid agonist, and its effect on u receptor is weak. Therefore, u receptor related nausea, vomiting, dizziness, headache, drowsiness, restlessness, pruritus, pruritus, nausea, vomiting, dizziness, headache, drowsiness, restlessness, pruritus, nausea, vomiting, dizziness, headache, drowsiness, restlessness, pruritus, nausea, vomiting, dizziness, headache The incidence of adverse reactions such as urinary retention decreased significantly * [14]. Based on the advantages and

disadvantages of opioid agonists and antagonists, Cepeda MS [15] and firouzian a [16] pointed out that opioid agonists and antagonists can achieve stronger analgesia and reduce the adverse reactions of opioid drugs when the drug ratio is right. Therefore, it is very important to find a method of medication that does not affect the analgesic effect but also reduces the side effects of drugs. On the one hand, it is necessary to reduce visceral pain and minimize side effects.

Some studies have found that when an appropriate amount of nalbuphine combined with μ receptor agonists can produce good analgesic effect and reduce adverse reactions [17, 18]. Objective to evaluate the optimal dosage of nabufen and sufentanil for PCIA after gynecological laparoscopic surgery. The results showed that the analgesic effect of low-dose nalbuphine combined with sufentanil in group B did not change. However, the moderate dose and high-dose combination of nalbuphine and sufentanil significantly reduced the incidence of opioid related side effects and significantly enhanced the analgesic effect of opioids. This is consistent with the research results of Luo Chong [19] that 1 mg / kg of nabufen combined with 1 μ g / kg sufentanil for postoperative analgesia in patients with laparoscopic radical hysterectomy for cervical cancer can reduce the dosage of strong opioids, effectively relieve the pain of patients and have no other serious complications. However, compared with group C, there was no significant difference in analgesic effect and moderate dose of nabufen in group D, but the adverse reactions such as drowsiness and dizziness increased. This suggests that moderate dose of nabufen combined with sufentanil can be used as the best combination to prevent visceral pain after gynecological laparoscopic surgery.

Conclusions

In conclusion, the combination of sufentanil PCIA with medium dose of nabufen can not only enhance the analgesic effect of sufentanil, but also significantly reduce the incidence of opioid drug-related side effects such as nausea and vomiting, significantly improve the postoperative analgesia satisfaction of patients, and achieve a balance between the maximum analgesic effect and the minimum adverse reaction, so as to achieve high patient satisfaction and low economic burden ultimate goal.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the Affiliated Hospital of Guangdong Medical University with the reference number PJ2019-061and signed the informed consent before operation. The trial was registered prior to patient enrollment at clinicaltrials.gov (Clinical study for the efficacy and safety of naborphine and sufentanil in the prevention of visceral pain after gynecological laparoscopic surgery: a random, double-blind and parallel control study , Principal investigator:GU Xiao-Xia , Date of registration:10 August 2019). Trial's clinical trial registration number is ChiCTR1900025076.

All participants were informed and asked for written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study will be available from the corresponding author on reasonable request.

Competing interests

There is no economic interest or conflict of interest exists.

Funding

This study was funded by National Natural Science Foundation of China. Liangqing Zhang is the project's host and the corresponding author of this paper. He also helped protocol writing, interpretation of results and reviewed the manuscript.

Authors' Contributions

Xx G and Jj W are Co-First Author,participated in protocol writing, collecting data, statistical analysis, interpretation of results and manuscript writing. Hh L and J M helped collection of cases, essay writing.Y L and P P participated in protocol writing, interpretation of results and manuscript writing Xj T and Lq Zdid the statistical analysis and reviewed the manuscript. All authors read and approved the final manuscript.

Acknowledgements

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