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Review Article

Propofol combined with remifentanil relieves pain after transabdominal hysterectomy and reduces its effects on heart rate

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Abstract: Objective: This study aimed to explore the effects of propofol combined with remifentanil during transabdominal hysterectomy (TAH). Methods: Altogether 110 patients with hysteromyoma who underwent TAH at The People's Hospital of Huaiyin from July 2017 to December 2018 were enrolled. Among them, 53 cases in Group A were treated with fentanyl combined with propofol, while other 57 cases in Group B were treated with remifentanil combined with propofol during operation. Their surgical conditions, hemodynamics, pain, and cognitive state were observed. Enzyme-linked immunosorbent assay (ELISA) was used to observe inflammatory cytokine levels and adverse reactions at different time periods. Results: Compared with those in Group A, patients in Group B had shorter consciousness recovery time and awake time ($P<0.05$), and better hemodynamics ($P<0.05$). After treatment, the pain score and the cognitive state in Group B were better than those in Group A ($P<0.05$). Compared with those in Group A, patients in Group B had lower inflammatory cytokine levels ($P<0.05$), and lower total incidence of adverse reactions ($P<0.05$). Conclusion: Propofol combined with remifentanil is safe and effective during TAH.

Keywords: Propofol, remifentanil, TAH, hysteromyoma, postoperative pain, hemodynamics

Introduction

As a common benign uterine smooth muscle tumor composed of monoclonal smooth muscle cells of myometrium [1, 2], hysteromyoma has adverse effects on patient fertility and causes other diseases [3]. With an incidence of 70-80% [4], the disease may indirectly affect patients' quality of life although it is usually asymptomatic [5]. At present, hysterectomy is an effective method for the treatment of hysteromyoma [6], and the uterus can be reserved according to the patients' own opinions [7]. Transabdominal hysterectomy (TAH), one of the operative methods, is carried out in the abdomen, and usually causes patients to suffer obvious pain [8], which has a negative effect on their recovery. Although many clinical attempts have been made to relieve postoperative pain, there is no universal method to control it.

Propofol is an intravenous hypnotic agent used to induce and maintain sedation and general anesthesia [9, 10], interacting with γ-aminobutyric acid A receptor in the central nervous system [11]. This drug is widely used in clinical practice due to its good anesthetic effect, but it often reversibly leads to loss of consciousness [12]. Additionally, it may result in some potential and well-known side effects [13]. Remifentanil, which is a short-acting μ receptor opioid agonist [14], is characterized by the predictable and rapid counteraction of non-specific esterase in blood and other tissues to the side effects through its metabolism [15]. A related report has shown that remifentanil combined with intravenous or volatile hypnotics is generally effective in reducing hemodynamics, intraoperative autonomic and somatic responses, and postoperative parameter recovery [16]. Therefore, the role of propofol combined with remifentanil during TAH was explored in this study.

Materials and methods

General information

A total of 110 patients with hysteromyoma in the People's Hospital of Huaiyin from July 2017

to December 2018 were enrolled. Among them, 53 patients in Group A were treated with fentanyl combined with propofol during operation, with an average age of 38.59±4.69 years and an average weight of 58.42±6.24 kg. Other 57 cases in Group B were treated with remifentanil combined with propofol, with an average age of 39.68±4.53 years and an average weight of 57.14±5.79 kg.

Inclusion and exclusion criteria

Inclusion criteria were as follows: patients who were diagnosed with hysteromyoma had complete data. In this study that was approved by the Medical Ethics Committee of The people's Hospital of Huaiyin, all patients and their families were informed and signed the informed consent form.

Exclusion criteria were as follows: patients with mental disorders; patients with major blood diseases; patients allergic to drugs used in this study; patients with severe hepatic and renal insufficiency.

Methods

All patients fasted before the operation. The radial artery was punctured and the venous access was established before anesthesia. Patients in Group A were slowly and intravenously infused with fentanyl (Yichang Humanwell Pharmaceutical Co., Ltd., SFDA approval number: H42022076) with a dose of 1 μg/kg, while those in Group B were intravenously infused with remifentanil (Yichang Humanwell Pharmaceutical Co., Ltd., SFDA approval number: H20030197) with a dose of 0.5 μg/kg. Two minutes later, the patients in both groups were slowly and intravenously infused with propofol (Jiangsu Enhua Pharmaceutical Group Co., Ltd., SFDA approval number: H20123138) with a dose of 1 mg/kg. After being under anesthesia, the patients were pumped with propofol at 6 mg/kg·h for anesthesia until the operation was finished.

Outcome measures

(1) The heart rate (HR) and the mean arterial pressure (MAP) before anesthesia (T0), at 30 min after anesthesia (T1), and after operation (T2) were observed in the two groups. (2) The Visual Analogue Scale (VAS) [17] was used to compare the pain scores between the two groups after treatment, with a score ranging from 0 to 10 points. The score was positively correlated with pain degree. (3) The Mini-Mental State Examination (MMSE) [18] was used to evaluate the cognitive function of patients before and after operation, with a full score of 30 points. The score was positively correlated with cognitive function. (4) Venous blood (5 mL) was drawn from patients in the two groups before, during, and after the operation. After allowed to stand for 20 min, the blood was centrifuged in a centrifuge (10×g at 4°C for 15 min, Beijing BMH Instruments Co., Ltd.) to separate serum, which was quickly frozen in liquid nitrogen and then stored at -80°C for later use. The levels of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were detected by enzyme-linked immunosorbent assay (ELISA) (Suzhou ELSBIO Biotechnology Co., Ltd.) according to the instructions.

Statistical methods

SPSS 21.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Measurement data were expressed by mean ± standard deviation ($\bar{x} \pm sd$), and its comparison between groups was analyzed by t test. Count data were expressed by n (%), and its comparison between groups was analyzed by chi-square test, and the comparison between multiple groups was analyzed by F test. $P<0.05$ indicated a statistically significant difference.

Results

Comparison of general information

There was no difference between Groups A and B in general information such as self-condition and basic symptoms ($P<0.05$) (**Table 1**).

Comparison of surgical conditions

The operative time in Group A and Group B was respectively 95.24±8.48 min and 96.13±9.32 min, without significant difference between the two groups ($P>0.05$). The postoperative consciousness recovery time in Group A (13.44±2.41 min) was significantly longer than that in Group B (9.58±1.39 min) ($P<0.05$). The postoperative awake time in Group A

Table 1. General information ($\bar{x} \pm sd$) [n (%)]

Categories	Group A (n=53)	Group B (n=57)	t/χ^2 value	*P* value
Age (Years)	38.59±4.69	39.68±4.53	1.240	0.217
Body weight (kg)	58.42±6.24	57.14±5.79	1.116	0.266
Place of residence			0.273	0.601
Countryside	24 (45.28)	23 (40.35)		
City	29 (54.72)	34 (59.65)		
Educational history			0.441	0.506
Below senior high school	17 (32.08)	15 (26.32)		
Above senior high school	36 (67.92)	42 (73.68)		
Nationality			1.183	0.276
Han	46 (86.79)	45 (78.94)		
Ethnic minorities	7 (13.21)	12 (21.05)		
Economic level			1.368	0.504
Poor	13 (24.53)	9 (15.79)		
Well-to-do	24 (45.28)	30 (52.63)		
Rich	16 (30.19)	18 (31.58)		
History of drinking			0.251	0.616
Yes	22 (41.51)	21 (36.84)		
No	31 (58.49)	36 (63.16)		
History of smoking			0.507	0.477
Yes	24 (45.28)	22 (38.60)		
No	29 (54.72)	35 (61.40)		
Obesity			0.796	0.372
Yes	30 (56.60)	37 (64.91)		
No	23 (43.40)	20 (35.09)		
Symptoms			1.523	0.677
Hemorrhage	17 (32.08)	15 (26.32)		
Symptom of oppression	15 (28.30)	18 (31.58)		
Pain	9 (16.98)	14 (24.56)		
Abortion	12 (22.64)	10 (17.54)		

(19.54±3.58 min) was significantly longer than that in Group B (12.39±1.37 min) (P<0.05). This indicates that propofol combined with remifentanil can restore the patients' postoperative awareness faster. See **Figure 1**.

Changes in hemodynamic indices

HR in Group A was 70.14±9.54 times/min at T0, 87.54±10.38 times/min at T1, and 103.48±11.24 times/min at T2. HR in Group B was 71.37±9.67 times/min at T0, 75.33±10.34 times/min at T1, and 77.23±10.32 times/min at T2. There was no difference in HR between Groups A and B at T0 (P>0.05). From T1 to T2, HR in Group B was significantly lower than that in Group A (P<0.05). See **Figure 2**. MAP in Group A was 91.38±9.32 mmHg at T0, 109.54±10.22 mmHg at T1, and 118.27±10.34 mmHg at T2. MAP in Group B was 92.42±10.13 mmHg at T0, 95.34±10.43 mmHg at T1, and 97.48±10.65 mmHg at T2. There was no difference in MAP between Groups A and B at T0 (P>0.05). From T1 to T2, MAP in Group B was significantly lower than that in Group A (P<0.05). This indicates that propofol combined with remifentanil has a slighter effect on the patients' hemodynamics. See **Figure 3**.

Comparison of pain score

After treatment, VAS score in Group A (4.59±2.42 points) was significantly higher than that in Group B (2.68±1.34 points) (P<0.05), indicating that the patient pain in Group A after treatment was relatively mild. See **Figure 4**.

Comparison of cognitive state

MMSE scores in Group A before and after treatment were 28.33±1.43 points and 22.18±1.89 points, respectively. The scores in Group B before and after treatment were 28.58±1.47 points and 26.58±1.38 points, respectively. After treatment, the cognitive state of patients in the two groups obviously recovered (P<0.05). Before treatment, there was no difference in the cognitive state between the two groups (P>0.05). After treatment, the cognitive state in Group B was better than that in Group A (P<0.05). This indicates that propofol combined with remifentanil can reduce the patients' cognitive dysfunction. See **Figure 5**.

Comparison of inflammatory cytokines

IL-6 levels in Groups A and B before operation were 49.38±4.58 ng/L and 50.24±4.35 ng/L,

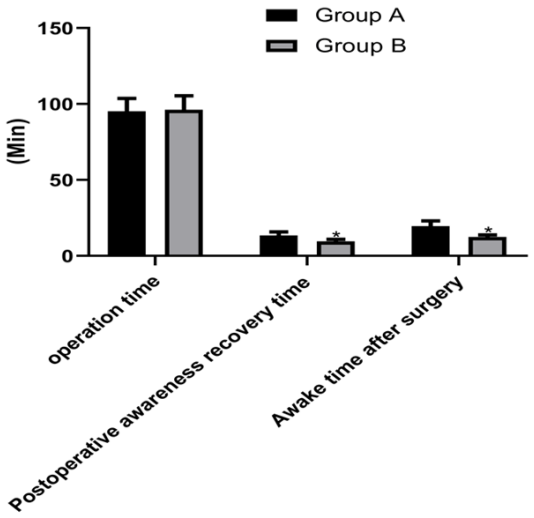

Figure 1. Comparison of surgical conditions. There was no significant difference in operative time between Groups A and B (P>0.05). The postoperative consciousness recovery time in Group B was significantly shorter than that in Group A. The postoperative awake time in Group B was significantly shorter than that in Group A. Note: *indicates P<0.05 when compared with that in Group A.

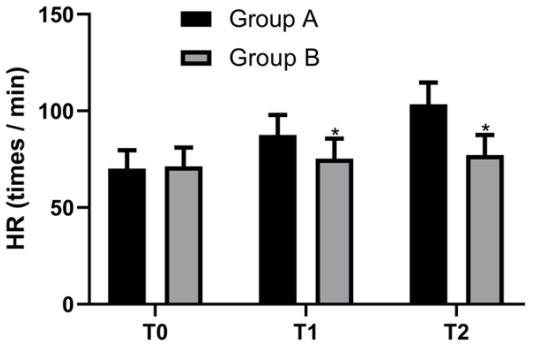

Figure 2. Changes in HR at different time periods. There was no difference in HR between Groups A and B at T0 (P>0.05). From T1 to T2, HR in Group B was significantly lower than that in Group A (P<0.05). Note: *indicates P<0.05 when compared with that in Group A.

respectively. The levels during operation were 118.32±9.42 ng/L and 83.27±6.36 ng/L, respectively. The levels after operation were 94.43±8.38 ng/L and 72.55±5.28 ng/L, respectively. TNF-α levels before operation were 21.46±3.27 ng/L and 22.14±3.26 ng/L, respectively. The levels during operation were 58.22±5.24 ng/L and 46.43±4.37 ng/L, respectively. The levels after operation were 47.54±4.25 ng/L and 34.27±3.58 ng/L, respectively. There were no differences in IL-6 and TNF-α levels before operation between the

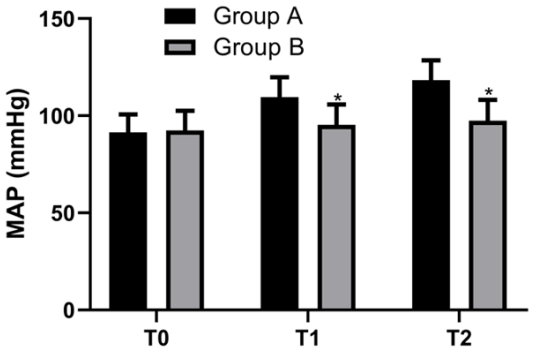

Figure 3. Changes in MAP at different time periods. There was no difference in MAP between Groups A and B at T0 (P>0.05). From T1 to T2, MAP in Group B was significantly lower than that in Group A (P<0.05). Note: *indicates P<0.05 when compared with that in Group A.

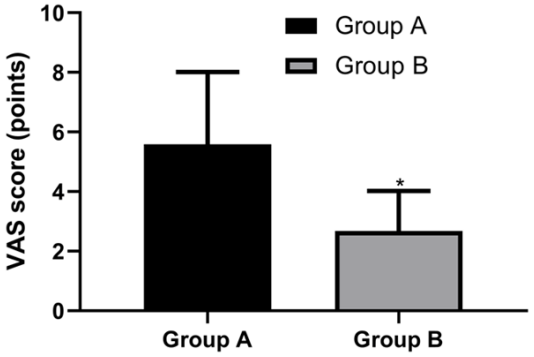

Figure 4. Comparison of postoperative pain score. VAS score in Group B was significantly lower than that in Group A after treatment (P<0.05). Note: *indicates P<0.05 when compared with that in Group A.

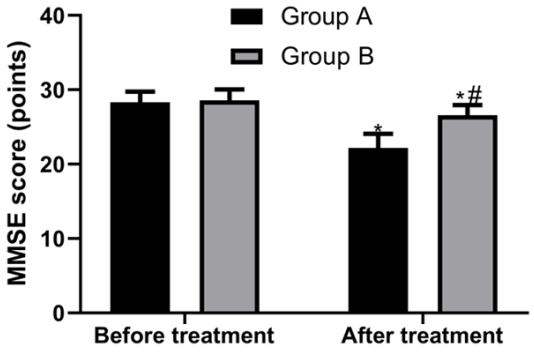

Figure 5. Comparison of cognitive state before and after treatment. After treatment, the cognitive state of patients in the two groups obviously recovered (P<0.05). Before treatment, there was no difference in the cognitive state between the two groups (P>0.05). After treatment, the cognitive state in Group B was better than that in Group A (P<0.05). Note: *indicates P<0.05 when compared with that in the same group before treatment. #indicates P<0.05 when compared with that in Group A.

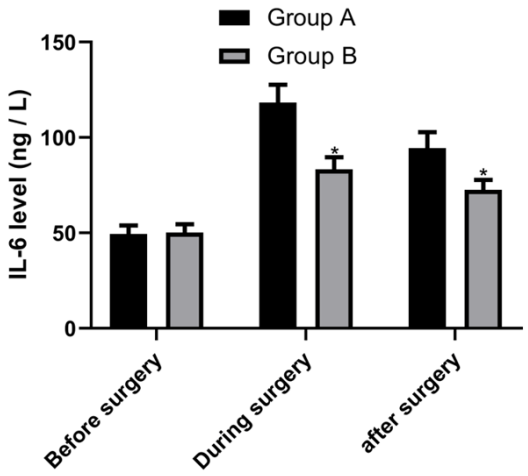

Figure 6. Comparison of IL-6 levels at different time periods. There was no difference in serum IL-6 level before operation between Groups A and B (P>0.05), but the levels in Group B during and after operation were significantly lower than those in Group A (P<0.05). Note: a indicates P<0.05 when compared with that in the same group before operation; b indicates P<0.05 when compared with that in the same group during operation; c indicates P<0.05 when compared with that in Group A.

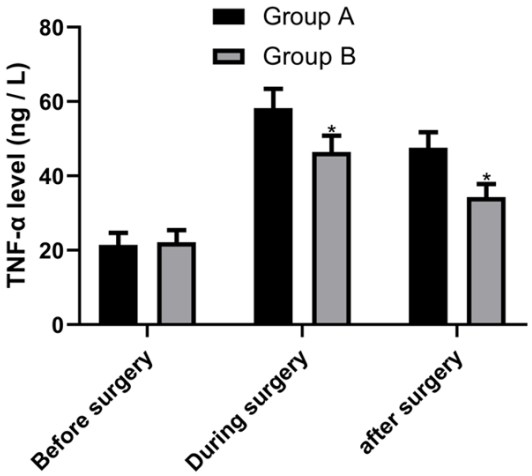

Figure 7. Comparison of TNF-α levels at different time periods. There was no difference in serum TNF-α level before operation between Groups A and B (P>0.05), but the levels in Group B during and after operation were significantly lower than those in Group A (P<0.05). Note: a indicates P<0.05 when compared with that in the same group before operation; b indicates P<0.05 when compared with that in the same group during operation; c indicates P<0.05 when compared with that in Group A.

two groups (P>0.05), but the levels in Group B during and after operation were significantly lower than those in Group A (P<0.05). This indicates that propofol combined with remifentanil can reduce the incidence of inflammation greater. See **Figures 6** and **7**.

Comparison of adverse reactions

The total incidence of adverse reactions in Group A (28.30%) was significantly higher than that in Group B (10.53%) (P<0.05). This indicates that propofol combined with remifentanil causes fewer adverse reactions. See **Table 2**.

Discussion

Propofol is currently proven to cause cognitive dysfunction in adults [19]. Therefore, in this study, the cognitive state of patients was observed at different time periods. The results showed that the cognitive state in Group B was better than that in Group A after treatment, suggesting that propofol combined with remifentanil causes less nerve injury. The reason for this result may also be that remifentanil has sedative and analgesic effects during the placement of local anesthesia block, and is combined with local anesthesia and airway nerve block, which may help to reduce reflex responses and promote “awake” fibrotic intubation [20]. This may also be the reason why the consciousness recovery time and awake time in Group B were shorter than those in Group A. There is a study showing that the target-controlled infusion of the combined drugs has hypnotic and analgesic effects, and can quickly recover and therefore enable early evaluation of postoperative neurological function [21]. HR is a non-stationary signal, whose changes may include indicators of current diseases or warnings about impending heart disease [22]. The detection of blood pressure also guides the treatment [23]. Therefore, it is essential to detect the hemodynamics of patients during operation, which is also convenient to adjust the medication for them. In this study, the hemodynamics in Group B was better than that in Group A after operation, which shows that propofol combined with remifentanil has few effects on hemodynamics. According to a related report, remifentanil can better control hemodynamics and significantly reduce the incidence of tachycardia and hypertension compared with fentanyl [24].

Table 2. Comparison of adverse reactions [n (%)]

Adverse reactions	Group A (n=53)	Group B (n=57)	X^2	P
Lethargy	2 (3.77)	2 (3.51)	-	-
Dizzy	3 (5.66)	1 (1.75)	-	-
Fever	1 (1.89)	1 (1.75)	-	-
Rash	2 (3.77)	1 (1.75)	-	-
Diarrhea	3 (5.66)	0 (0.00)	-	-
Nausea	1 (1.89)	0 (0.00)	-	-
Vomiting	1 (1.89)	0 (0.00)	-	-
Limb weakness	2 (3.77)	1 (1.75)	-	-
Total incidence	15 (28.30)	6 (10.53)	5.618	0.017

Trauma caused by surgery may cause inflammatory responses aiming to limit further injury. In addition, a study has shown that the concentrations of relevant cytokines will increase within half an hour after injury [25]. As a pro-inflammatory cytokine [26], IL-6 widely affects cells of the immune and non-immune systems, and usually shows hormone-like characteristics that affect steady-state processes [27]. TNF-α is a pleiotropic cytokine with many functions such as maintaining homeostasis and inducing inflammation [28], playing an important role in normal and pathophysiological processes [29]. A study has shown that the surgical trauma of patients undergoing TAH may induce stress responses and inflammatory responses harmful to rehabilitation, which is manifested by increasing blood pressure, HR, and blood glucose, as well as the release of inflammatory cytokines such as IL-6 and TNF-α [30]. Therefore, changes in related inflammatory cytokines were observed in this study, and the results showed that IL-6 and TNF-α levels in Group B were significantly lower than those in Group A. This reveals that propofol combined with remifentanil is more effective in inhibiting inflammatory cytokines. Moreover, we observed the adverse reactions in the two groups, and the results showed that the adverse reactions in Group B were fewer than those in Group A. Accordingly, it is suspected that the more effective inhibitory effect of the combination reduces the side effects. A similar study has shown that the controlled infusion of the two drugs for moderate sedation is feasible, safe, and highly satisfactory [31].

There are still deficiencies in this study. For example, we didn't treat the drugs separately or compare them with different administration methods. Therefore, we will continue to update the research in the future.

In summary, propofol combined with remifentanil is safe and effective during TAH.

Disclosure of conflict of interest

None.

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