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Original Research Article

Effect of chloroprocaine combined with morphine on analgesia, adverse reactions and dynamic changes in inflammation in patients receiving TURP

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Abstract

Purpose: *To investigate the influence of chloroprocaine combined with morphine on the analgesic effects, adverse reactions and inflammation factors in patients receiving transurethral resection of the prostate (TURP).*
Methods: *A total of 80 patients with benign prostatic hyperplasia (BPH) in the Fourth Medical Center of Chinese PLA General Hospital, Beijing 100048, China, were divided into morphine group and combination-therapy group (morphine combined with chloroprocaine). Pain index, changes in inflammatory factors and incidence of adverse reactions in the two groups of patients were assessed.*
Results: *The morphine group and combination-therapy group showed basic profile prior to the treatments. Visual Analogue Scale (VAS) scores before operation and 6 h after operation in the morphine group were similar to those in the combination-therapy group, but the scores at 12, 24 and 48 h after operation in the combination-therapy group were significantly lower than those in the morphine group. Similarly, the combination-therapy group showed lower levels of substance P (SP) and bradykinin (BK) at 12, 24 and 48 h after operation than the morphine group ($p < 0.05$). Both groups exhibited similar levels of serum inflammatory factors before the operation, but the levels decreased in the combination-therapy group when compared with those in the morphine group after operation ($p < 0.05$). The combination-therapy group also showed a lower incidence of adverse reactions than the morphine group.*
Conclusion: *Chloroprocaine combined with morphine effectively ameliorates postoperative pain, lowers secretion of tumor necrosis factor-alpha (TNF-α) and interleukin-10 (IL-10), and decreases the incidence of postoperative adverse reactions, thus affording a high level of safety after operation.*

Keywords: *Benign prostatic hyperplasia, Morphine, Chloroprocaine, Analgesia, Inflammation, Adverse reactions*

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common urinary system disease, with urodynia and frequent micturition as the common clinical complications in patients. There are many therapeutic methods for treating BPH, including oral medication [1,2]. However, surgeries are

more frequently employed in clinical treatment of BPH. Although transurethral resection of the prostate (TURP) has been applied in the clinical treatment of BPH, majority of BPH patients manifest fairly high incidence of pain, urethrospasm and other postoperative complications, poor perception after operation and extended bladder irrigation and extubation time, due to advanced age and insufficient immunity. Thus, prognosis and quality of life are seriously affected [3,4]. Therefore, ameliorating the pain threshold, adverse reactions and dynamic state of inflammation of the patients after operation is of crucial importance.

Chloroprocaine, a kind of amide anesthesia first approved and marketed in China in 2002, is often used for local anesthesia, general anesthesia and postoperative analgesia, without apparent toxic side-effects after operation, and particularly has few adverse reactions in the nervous system. Morphine administered epidurally after operation usually produces good effects and favorable analgesic effects as a natural opium alkaloid. However, it was discovered in previous studies that morphine has a certain impact on the respiratory system and cardiovascular function of patients, and affects multiple chemoreceptor zones in the body, thereby triggering various adverse reactions in some patients [5,6]. Generally, morphine is applied together with other anesthetics in clinical treatment to reduce the patient's adverse reactions. The influence of morphine combined with chloroprocaine on the prognosis of patients undergoing TURP has not been determined yet. Therefore, a number of BPH patients who needed TURP were analyzed, and the changes in postoperative pain, inflammatory responses and postoperative complications were studied in this manuscript.

METHODS

Basic profile of subjects

Eighty BPH patients admitted to and treated in The Fourth Medical Center of Chinese PLA General Hospital, Beijing, China I were selected. The mean age was 63.25 ± 9.37 years, and the average weight was 60.46 ± 8.48 kg. All the patients were assigned into morphine group (n = 40) and combination-therapy group (n = 40) according to different analgesia modes after operation (Table 1). The Ethics Committee of the Fourth Medical Center of Chinese PLA General Hospital approved this study and all patients signed informed consent.

Inclusion and exclusion criteria

Inclusion criteria

(1) Patients at ASA I-II grade, (2) those with normal metabolism of liver function, and (3) those who and whose families signed the informed consent.

Exclusion criteria

(1) Patients with cognitive impairment, (2) those who took non-steroidal anti-inflammatory drugs within 30 days before operation, or (3) those with chronic pain.

Anesthetic methods and analgesic regimens

Intravenous lines were established before operation, through which phenobarbital was injected. Thirty minutes later, with the patients in left lateral position, combined spinal-epidural analgesia at the L3-4 level was performed. Bupivacaine and glucose solution were injected into the subarachnoid space, the epidural catheter was inserted toward the head, and the blood pressure was controlled at 120 - 90 mmHg. Finally, a mechanical analgesia pump at an injection rate of 2 mL/h was utilized for analgesia. As for the patients in the morphine group, 40 μg/mL morphine was infused into the analgesia pump, while morphine and chloroprocaine were added to the analgesia pump in the combination-therapy group. Moreover, the patients and their family members were instructed to report to the physicians timely if they experienced unbearable pain and discomfort. Besides, the operation time, continuous bladder irrigation time, urinary catheter in-dwelling time and length of hospital stay of the two groups of patients were recorded.

Visual Analogue Scale (VAS) scoring

The VAS scoring was performed before operation and at 6, 12, 24 and 48 h after operation, and the severity of pain was analyzed,

Table 1: Baseline data

Group	Mean age (years)	Mean weight (kg)	Mean course (month)
Morphine (n = 40)	46.12±9.05	60.39±.38	7.25±2.79
Combination therapy (n= 40)	45.39±10.12	61.05±8.49	7.34±2.87
t	0.341	0.349	0.142
P-value	0.734	0.742	0.887

with a score ranging from 0 point (no pain) to 10 points (severe pain). Besides, 3 mL of peripheral blood was drawn at corresponding time points to determine the levels of substance P (SP) and bradykinin (BK) *via* enzyme-linked immunosorbent assay (ELISA, R&D Systems, Minneapolis, MN, USA).

Determination of serum levels of tumor necrosis factor-alpha (TNF-α) and interleukin-10 (IL-10)

The peripheral blood (3 mL) was collected in the early morning before and after operation and then centrifuged. ELISA was performed according to the kit manufacturer's instructions.

Incidence of adverse reactions

Gastrointestinal reaction, nervous system reaction, respiratory depression and arrhythmia occurring in the patients after operation were recorded.

Statistical analysis

SPSS statistical analysis software (version 26.0) software was employed for analysis, and *t*-test was performed. The enumeration data are expressed as (mean **±** SD) while measurement data are presented were analyzed by χ^2. $P < 0.05$ indicated statistically significant difference.

RESULTS

Basic profile of patients

Morphine group and combination-therapy group had similar general operation data in terms of time and conditions ($p > 0.05$) (Table 2).

VAS scores

The VAS scores before operation and at 6 h after operation in morphine group were similar to those in combination-therapy group ($p > 0.05$), but the scores at 12, 24 and 48 h after operation in combination-therapy group were lower than those in morphine group ($p < 0.05$) (Table 3).

Changes in the levels of pain before and after operation

SP and BK manifested close levels in both groups before operation and at 6 h after operation ($p > 0.05$), while the combination-therapy group had lower levels of SP and BK at 12, 24 and 48 h after operation than morphine group ($p < 0.05$; (Tables 4-5).

Table 2: Basic profile of patients in the two groups

Group	Operation time (min)	Continuous bladder irrigation time (d)	Urinary catheter in-dwelling time (d)	Length of hospital stay (d)
Morphine (n = 40)	60.16 ± 9.05	2.09 ± 0.38	3.21 ± 1.73	7.43 ± 2.36
Combination-therapy (n = 40)	59.39 ± 10.12	2.05 ± 0.49	3.14 ± 1.67	7.29 ± 2.53
t	0.358	0.408	0.184	0.256
P-value	0.721	0.684	0.854	0.798

Table 3: VAS scores at different time points after operation in the two groups

Group	Before operation	6 h	12 h	24 h	48 h
Morphine (n = 40)	2.45 ± 1.32	5.56 ± 2.12	7.35 ± 3.75	7.68 ± 2.59	7.79 ± 2.91
Combination-therapy (n = 40)	2.39 ± 1.41	5.27 ± 2.31	3.66 ± 2.56*	3.88 ± 2.27*	3.75 ± 2.38*
T	0.249	0.585	5.141	6.978	6.797
P-value	0.776	0.561	0.002	< 0.001	< 0.001

**P* < 0.05 *vs*. morphine group

Table 4: Changes in SP level in both groups before and after operation

Group	Before operation	6 h	12 h	24 h	48 h
Morphine (n = 40)	87.67 ± 10.24	110.45 ± 12.48	135.78 ± 14.13	187.39 ± 20.76	176.49 ± 19.56
Combination-therapy (n=40)	88.21 ± 9.87	111.09 ± 11.89	115.67 ± 12.89*	130.45 ± 15.98*	124.65 ± 14.76*
T	0.225	0.447	11.455	15.309	12.336
P-value	0.884	0.127	< 0.001	< 0.001	< 0.001

**P* < 0.05, *vs*. morphine group

Table 5: Changes in BK level in both groups before and after operation

Group	Before operation	6 h	12 h	24 h	48 h
Morphine (n = 40)	52.78 ± 7.54	54.38 ± 8.12	93.35 ± 11.23	121.09 ±14.37	110.72 ± 13.95
Combination-therapy (n = 40)	53.23 ± 6.49	55.21 ± 7.94	68.32 ± 8.78*	88.45 ± 13.07*	79.33 ± 13.88*
T	0.589	1.044	9.035	10.774	9.438
P-value	0.472	0.227	< 0.001	< 0.001	< 0.001

**P* < 0.05, *vs*. morphine group

Comparisons of serum levels of inflammatory factors before and after operation

Both groups exhibited similar levels of serum inflammatory factors before operation (p>0.05), but those levels were decreased in combination-therapy group compared with those in morphine group after operation (p<0.05) (Table 6).

Table 6: Comparison of serum inflammatory factors between the two groups

Group	Time	TNF-α	IL-10
Morphine (n = 40)	Before operation	14.67 ± 2.13	18.45 ± 2.33
Combination-therapy (n = 40)		15.12 ± 1.89	18.39 ± 2.41
T		1.002	0.113
P		0.319	0.912
Morphine group (n = 40)	After operation	46.89 ± 6.45#	61.89 ± 8.45#
Combination-therapy group (n = 40)		24.78 ± 3.67*#	31.46 ± 5.46*#
T		18.841	19.142
P		< 0.001	< 0.001

**p*<0.05 *vs*. morphine group; #*p*<0.05, *vs.* before operation

Incidence of adverse reactions

There were 12 patients in the morphine group (30 %) and 4 (10 %) patients in combination-therapy group that experienced adverse reactions (p < 0.05) as shown in Table 7.

Table 7: Comparison of adverse reactions between the two groups

Group	Respiratory depression	Nausea and vomiting	Pruritus	Total incidence rate (%)
Morphine group (n = 40)	2 (5.00)	5 (12.50)	5 (12.50)	12 (30.00)
Combination-therapy group (n = 40)	0 (0.00)	3 (7.50)	1 (2.50)	4 (10.00)*
χ^2				10.007
P-value				0.002

**P* <0.05 *vs.* morphine group

DISCUSSION

There are several of therapeutic methods for BPH, such as traditional operations, drug therapies and minimal invasion. TURP is a preferred treatment method for the operation for BPH patients, which is characterized by small traumas and rapid recovery. However, complications such as postoperative bleeding still occur in TURP [7,8]. Therefore, treatment of BPH patients with medicine intervention is important for alleviating postoperative pain, eliminating inflammation and ameliorating postoperative complications [9].

In this study, there were no differences in the of the patients, including operation time and operative hemorrhage between morphine group and combination-therapy group. Combination-therapy group had similar VAS scores before operation and at 6 h after operation but lower scores at 12, 24 and 48 h after operation compared with morphine group. Morphine, a natural opium alkaloid has desirable analgesic effects on the patients after operation [10]. As an ester-type local anesthetic, chloroprocaine hydrochloride belongs to short-term anesthetics with a short action time.

Benoit *et al* [11] demonstrated that chloroprocaine combined with morphine produces favorable postoperative analgesic effects on the patients undergoing TURP. Farag *et al* [12] illustrated that chloroprocaine can prominently relieve the bladder spasm and wound pain in the patients after TURP and reduce morphine-induced postoperative complications [13]. Zhang *et al* [14] revealed that morphine combined with chloroprocaine is able to inhibit the expression of pain mediums after BPH surgery more effectively. In the present study, it was discovered that the levels of SP and BK in the combination-therapy group were close to those in the morphine group before operation and at 6 h after operation, but they declined in combination-therapy group at 12, 24 and 48 h after operation in comparison with those in the morphine group. SP is a type of tachykinin, which can act on adjacent tissues to induce pain after surgical trauma [15]. As a derivative of kallikrein action on kininogen, BK has a strong pain inducing ability and can bind to the tissues of the central nervous endings to stimulate nociceptive information transmission and arouse the pain sensation. The study of Plante *et al* [16] elaborated that the serum SP and BK levels were elevated remarkably after TURP, indicating that the surgical wound will induce the increased expressions of the two substances.

TNF-α, a crucial factor that promotes the development of inflammation, can mediate the activation of numerous inflammatory cells to enhance the inflammatory response. IL-10 is capable of repressing inflammation, but it can also lead to the overactivation of inflammatory response and aggravate the disease when its content reaches a certain level. According to the findings in this research, the raised expressions of the two factors in the serum in combination-therapy group might be related to postoperative stress response, but combination-therapy group displayed lower levels than morphine group, illustrating that morphine combined with chloroprocaine can efficiently inhibit the conjugation and secretion of inflammatory cells in the patients after operation [17]. It was demonstrated in the research of Varca *et al* [18] that morphine and chloroprocaine are able to decrease the release of inflammatory factors, relieve postoperative hyperalgesia and alleviate inflammatory response, which is consistent with the research results of Allegri *et al* [19].

There were fewer adverse reactions in combination-therapy group than those in the morphine group, indicating that morphine combined with chloroprocaine the high safety after operation. It is mainly manifested that the inhibitory effect of morphine on the respiratory system is strengthened along with the increased dose, but the incidence rate of gastrointestinal reaction is lowered when the patients are administered with chloroprocaine combined with morphine. The possible reason is that chloroprocaine can attenuate the side effects of morphine on visceral smooth muscles and reduce nausea and vomiting. All these results are in line with the findings of Sweet *et al* [20].

CONCLUSION

Chloroprocaine combined with morphine effectively ameliorates the postoperative pain, reduces the secretion of TNF-α and IL-10, decreases the incidence of postoperative adverse reactions, and affords high safety after operation, indicating its potential usefulness in clinical practice. However, further clinical trials are required to buttress this.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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