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Original Article

Clinical study on postoperative analgesic effects of preoperative use of dezocine in pelvic internal fixation of patients

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Abstract: Objective: To investigate the effects on patient s' postoperative pain and stress response with different doses of dezocine before pelvic operation, and evaluate the clinical effects of preventive analgesia with dezocine in pelvic operation. Methods: 80 patients underwent pelvic operation were selected and randomly divided into 4 groups (n=20): Group D1 (dezocine 0.1 mg/kg), Group D2 (dezocine 0.15 mg/kg), Group D3 (dezocine 0.20 mg/kg) and control group (Group C) (5 ml normal saline). Group D1, D2 and D3 were intravenously injected dezocine 15 min before anesthesia induction, while Group C was injected with 5 ml normal saline. The four groups used postoperative sulfentanil PCIA for analgesia. Levels of blood glucose (BG), C-reactive protein (CRP), TNF-α and IL-6 of each group were measured before treatment (T0), at the end of operation (T1), at 6 h after operation (T2) and at 24 h after operation (T3) respectively; operation time, recovery time and extubation time, postoperative VAS, postoperative sufentanil consumption, Ramsay score and side effects of each group were recorded. Results: (1) At T1 and T2, the blood glucose (BG) concentrations of Group D1, D2 and D3 were obviously lower than that of Group C, while Group D2 and D3 were lower than Group D1 (P<0.05). At T2 and T3, the CRP, IL-6 and TNF-α of Group D1, D2, D3 were distinctly lower than that of Group C, while Group D2 and D3 were lower than Group D1 (P<0.05). (2) Concerning the VAS of patients within 24 hours after operation, Group D1, D2, D3 were lower than Group C, and Group D2, D3 were lower than D1 (P<0.05). As for the postoperative dosage of sufentanil used in patients within 24 hours, Group D1, D2, D3 were lower than Group C, and D2, D3 were lower than D1 (p<0.05). (3) The recovery time and extubation time of Group D1, D2 and C were shorter than that of Group D3, and the difference was statistically significant (P<0.05). The Ramsay scores of Group D1, D2, and C at 2 hours postoperatively were lower than that of Group D3 (P<0.05), and the difference was statistically significant. (4) The cases of dizziness and drowsiness in Group D1, D2, D3 were less than that of Group D3 and the difference was statistically significant (P<0.05). Conclusion: (1) Dezocine used for preventive analgesia in pelvic operation can effectively inhibit stress response after operation. (2) Dezocine used for preventive analgesia in pelvic operation can distinctly reduce postoperative pain, improve postoperative analgesia satisfaction, and reduce the postoperative sufentanil consumption. (3) The most suitable dosage of dezocine for preventive analgesia in pelvic fracture surgery is 0.15 mg/kg with the least adverse reactions.

Keywords: Dezocine, pelvic surgery, preventive analgesia, stress response

Introduction

With the transformation of modern medical mode, exploration of ideal analgesic mode has important clinical significance to reduce postoperative pain and stimulative impact of surgical trauma to body at the maximum extent [1, 2]. In order to further improve the analgesic effect and reduce the occurrence of adverse reactions, it is advocated to adopt a balanced or multimode way, which including preemptive analgesia [3]. Preemptive analgesia, which is continuously used from pre-operation to post-operation with multi - mode analgesic methods, to eliminate the pain caused by surgical trauma, prevent and inhibit the sensitization of central and peripheral nerves [4]. Preemptive analgesia research on morphine, other opioids,

local anesthetics and nonsteroidal drugs was rich but the study of dezocine was relatively less [2, 5, 6]. Increasing the dose of dezocine will enhance the analgesic efficacy, but also will lead to adverse reactions of excessive sedation and respiratory depression in patients [7, 8]. 80 cases of patients underwent pelvic internal fixation from July 2014 to August 2015 in our hospital were selected in this research, applied with different doses of dezocine respectively before surgery, which intends to evaluate the effect of preemptive analgesia and the optimal dose of dezocine, and to provide reliable basis for clinical anesthesia and analgesia.

Materials and methods

Groups

This study was approved by hospital ethics committee and informed consent was signed by patients. 80 cases of patients underwent pelvic internal fixation were chosen, of which, 49 cases were male, 31 cases were female, ASA staged I-II, aged 20 to 60 years, and BMI was 16-25. Patients were randomly divided into 4 groups, with 20 cases in each group. Group D1 (dezocine 0.1 mg/kg), group D2 (dezocine 0.15 mg/kg), D3 group (dezocine 0.20 mg/kg), group C (normal saline 5 ml), all groups were given medicines 15 minutes before anesthesia induction. All patients were excluded from respiratory dysfunction, coronary heart disease, pepticulcer, asthma, severe liver and kidney function damage, history of cardiocerebrovascular diseases, history of long-term analgesic and sedative drugs application etc.

Anesthesia and analgesia methods

Patients were tracheal intubated after induction of anesthesia with midazolam 0.05 mg/kg, fentanyl 4 g/kg, vecuronium bromide 0.1 mg/kg and propofol 1.5 mg/kg. After intubation, pump infusion of propofol, remifentanil, cisatracurium to maintain anesthesia. Singly add fentanyl to maintain anesthesia during operation, and the total dose should not exceed 8 ug/kg; maintain the stability of hemodynamics. Stop adding fentanyl 1.5 hour before the end of surgery, and do not use muscle relaxant 30 minutes before the end of surgery. Before anesthesia induction (15 minutes), three experimental groups were given intravenous injection of dezocine, D1 was 0.1 mg/kg, D2 was 0.15 mg/kg, and D3 was 0.20 mg/kg, while group C was given intravenous injection of saline 5 ml. All patients used sufentanil for PCIA analgesia after operation.

Observation index

Separating plasma from 3 ml patients' peripheral venous blood, before the drug administration (T0), after operation (T1), 6 hours after operation (T2), and 24 hours after operation (T3) respectively; then draw appropriate amount to detect the instant BG concentration. The remaining was kept in refrigerator at -20°C to avoid repeated freezing and thawing. BG, CRP, IL-6 and TNF-α concentrations were detected by ELISA method after the samples were completely collected.

Operation time, recovery time, extubation time, and adverse reactions like nausea, vomiting, dizziness, drowsiness, respiratory depression, skin itch and others were recorded [9].

Pain score: VAS score method was adopted (0 point for completely painless, 10 points for unendurable pain), and pain scores of patients at 2 h, 6 h, 12 h and 24 h after operation were recorded [10].

Sedation score: the Ramsay score method was adopted (1 point for dysphoria, 2 points for quiet and cooperation, 3 points for sleepiness but can obey orders, 4 points for quick response to calls, 5 points for sleepiness and slow response to calls, and 6 points for deep sleep, no response to calls), sedation scores of patients at 2 h, 12 h, 6 h and 24 h after surgery were recorded [11].

Statistical analysis

All measurement data were expressed by mean ± standard deviation ($x \pm s$), and analyzed by SPSS I3.0. Measurement data were analyzed by repeated measurement analysis of variance, enumeration data were analyzed by X^2 test, and the satisfaction degree of analgesia in the treatment of preemptive analgesia was measured by rank sum test. The difference was statistically significant when $P<0.05$.

Results

General situation before anesthesia in four groups of patients

There was no significant difference ($P>0.05$) in gender, age, ASA, BMI, operation time, recovery

Table 1. General situation before anesthesia in four groups of patients

Group	Cases	Gender (Male/female)	Age (Years)	ASA (I/II)	BMI (kg/m^2)	SBP (mmHg)	HR (times/min)
D1	20	12/8	44.3±12.5	10/10	20.5±1.3	116.8±9.1	75.2±6.1
D2	20	13/7	42.5±11.8	9/11	21.2±1.8	117.5±8.6	76.1±6.3
D3	20	11/9	43.6±12.1	7/13	20.7±1.5	116.7±9.7	74.8±5.9
C	20	13/7	43.9±11.3	8/12	19.8±1.4	115.9±9.9	75.7±5.7

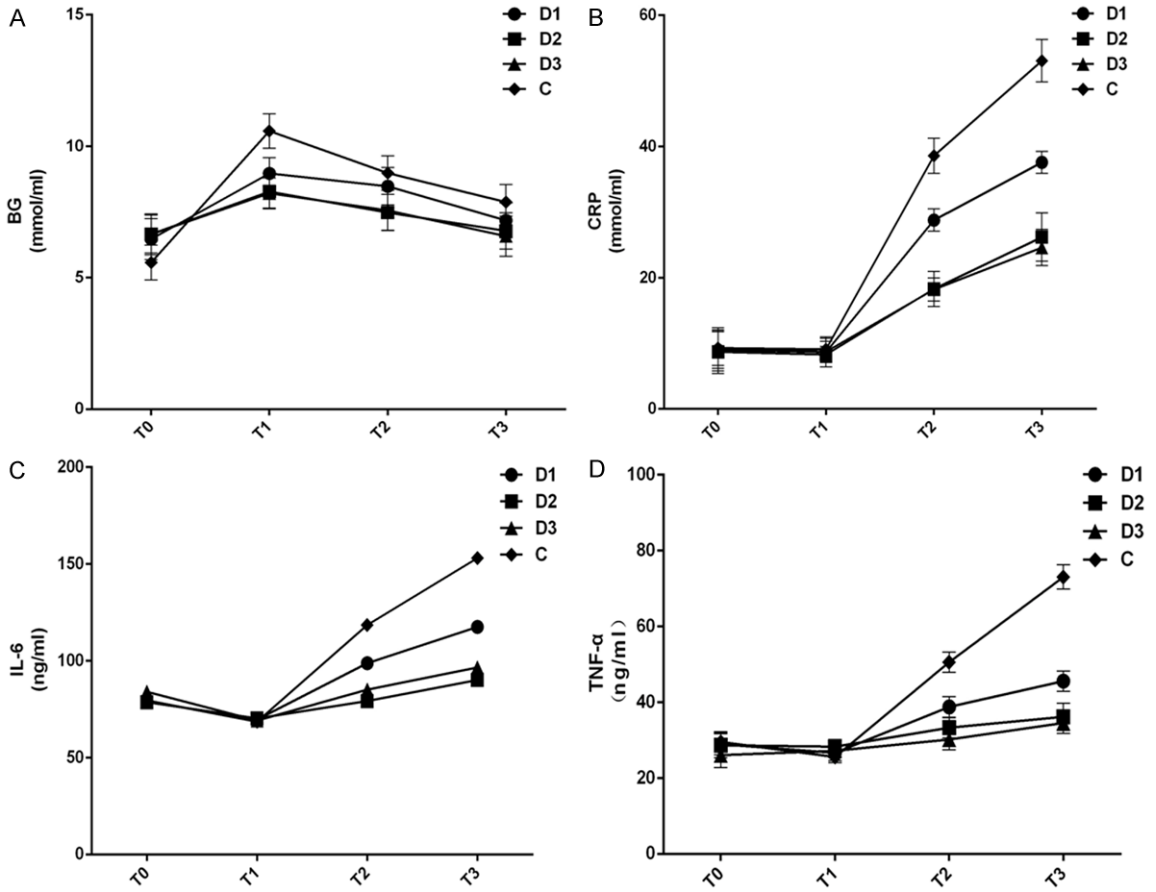

Figure 1. Change of stress response in four groups of patients. A: Changes of peri-operative BG in the four groups of patients; B: Changes of peri-operative CRP in the four groups of patients; C: Changes of peri-operative IL-6 in the four groups of patients; D: Changes of peri-operative TNF-α in the four groups of patients.

time and extubation time etc. between the four groups of patients (n=20) (See **Table 1**).

Changes of stress response in four groups of patients

Changes of blood glucose (BG) in patients during perioperation period: At T0, the blood glucose levels of the four groups were all in normal range, and the difference was not statistically significant (P>0.05). At T1 and T2, the blood glucose levels of group D1, D2 and D3 were significantly lower than that of group C (P<0.05), and D2 and D3 were significantly higher than those in D1 (P<0.05), while the difference between D2 and D3 was not statistically significant (P>0.05). At T3, the blood glucose levels of the four groups were returned to normal, and there was no significant difference between the four groups (P>0.05) (See **Figure 1A**).

Changes of serum CRP in four groups of patients during perioperative period: At T0 and T1, CRP concentrations in the 4 groups were all in normal range, and the difference was not statistically significant (P>0.05); at T2 and T3, CRP concentrations in group D1, D2, D3 were significantly lower than that in group C, and D2,

Table 2. VAS score comparison in four groups of patients (x±s)

Group	Postoperative 2 h	Postoperative 6 h	Postoperative 12 h	Postoperative 24 h
D1	3.5±1.1$^{\#,*,\Delta}$	2.8±1.3$^{\#,*,\Delta}$	2.6±1.8$^{\#,*,\Delta}$	2.3±1.1$^{\#,*,\Delta}$
D2	2.0±1.2$^{\#}$	2.1±1.1$^{\#}$	2.1±1.0$^{\#}$	1.9±1.0$^{\#}$
D3	2.0±1.2$^{\#}$	1.8±1.1$^{\#}$	1.4±1.0$^{\#}$	1.5±1.0$^{\#}$
C	4.3±2.1	3.5±1.9	3.4±2.0	4.3±2.2

Note: Compared with group C, $^{\#}$P<0.05; Compared with group D2, *P<0.05; Compared with group D3, $^{\Delta}$P<0.05.

Table 3. Postoperative sufentanil dosage at each time point in four grups of patients (μg) (x±s)

Group	Postoperative 2 h	Postoperative 6 h	Postoperative 12 h	Postoperative 24 h
D1	3.5±1.1$^{\#,*,\Delta}$	10.4±2.6$^{\#,*,\Delta}$	18.2±4.3$^{\#,*,\Delta}$	33.6±7.2$^{\#,*,\Delta}$
D2	2.5±1.4$^{\#}$	8.2±2.3$^{\#}$	15.7±5.1$^{\#}$	29.6±6.4$^{\#}$
D3	2.1±1.2$^{\#}$	7.9±2.1$^{\#}$	15.2±6.1$^{\#}$	28.9±6.9$^{\#}$
C	4.6±1.9	15.3±4.2	28.5±5.3	45.4±6.7

Note: Compared with group C, $^{\#}$P<0.05; Compared with group D2, *P<0.05; Compared with group D3, $^{\Delta}$P<0.05.

Table 4. Comparison of surgery time, recovery time and extubation time in four groups

Group	Operation time (min)	Recovery time (min)	Extubation time (min)
D1	149.2±8.5	6.4±1.1$^{\Delta}$	13.5±1.2$^{\Delta}$
D2	148.6±8.3	6.5±1.2$^{\Delta}$	13.7±1.1$^{\Delta}$
D3	147.9±8.2	8.5±1.4	15.6±1.4
C	150.1±8.7	6.4±0.9$^{\Delta}$	13.8±0.8$^{\Delta}$

Note: Compared with group D3, $^{\Delta}$P<0.05.

D3 was significantly lower than that in D1 (P<0.05), but there was no significant difference between D2 and D3 (P>0.05) (See **Figure 1B**).

The change of IL-6 concentration in four groups of patients during perioperative period: At T0 and T1, IL-6 concentrations of 4 groups were all in normal range, and the difference was not statistically significant (P>0.05); at T2 and T3, the IL-6 concentrations in group D1, D2 and D3 were significantly lower than that in group C, and D2, D3 was lower than D1 group (P<0.05), but there was no significant difference between D2 and D3 (P>0.05) (See **Figure 1C**).

The change of TNF-α concentration in four groups of patients during perioperative period: At T0 and T1, TNF-α concentrations of 4 groups were all in normal range, and there was no statistically significant difference (P>0.05); At T2 and T3, the TNF-α concentrations in group D1, D2 and D3 were lower than that in group C, and D2 and D3 was lower than group D1 (P<0.05), but there was no significant difference between D2 and D3 (P>0.05) (See **Figure 1D**).

Postoperative pain in four groups of patients

VAS score of postoperative pain in four groups of patients: Within 24 postoperative hours, the VAS score of group D1, D2 and D3 were lower than that of group C; group D2 and D3 was lower than group D1, and the difference was statistically significant (P< 0.05) (See **Table 2**).

The comparison of postoperative PCIA sufentanil consumption in four groups of patients: As for the postoperative PCIA sufentanil consumption in four groups of patients within 24 postoperative hours, group D1, D2 and D3 were lower than that of group C; D2 and D3 is lower than group D1, and the difference was statistically significant (P<0.05) (See **Table 3**).

Sedation in patients of four groups

Surgery time, awakening time and extubation time in four groups of patients: The comparison of operation time between the four groups had no statistical significance (P>0.05); the awakening time and extubation time in group D1, D2 and C was shorter than that of group D3, and the difference was statistically significant (P< 0.05), the difference between group D1, D2, and C was not statistically significant (P>0.05) (See **Table 4**).

Ramsay score of patients in four groups

At 2 hours after surgery, the Ramsay scores of group D1, D2 and C were lower than that of D3, and the difference was statistically significant (P<0.05). The difference of Ramsay scores at the other time points was not statistically significant (P>0.05) (See **Table 5**).

Postoperative adverse reactions in four groups of patients

The cases of dizziness and drowsiness in group D1, D2 and D3 were less than that of group D3, and the difference was statistically significant

Table 5. Ramsay scores in four groups of patients

Group	Postoperative 2 h	Postoperative 6 h	Postoperative 12 h	Postoperative 24 h
D1	2.4±0.9$^{\Delta}$	2.6±0.7	2.5±0.8	2.7±0.5
D2	2.6±0.8$^{\Delta}$	2.7±0.9	2.5±0.6	2.6±0.7
D3	3.5±1.1	2.8±0.9	2.7±0.5	2.5±0.4
C	2.3±0.7$^{\Delta}$	2.7±0.9	2.6±0.8	2.5±0.6

Note: Compared with group D3, $^{\Delta}P<0.05$.

Table 6. Comparison of postoperative adverse reactions in four groups of patients

Number of group	Cases	Nausea	Vomiting	Dizziness	Pruritus	Sleepiness
D1	20	2	1	1$^{\Delta}$	1	1$^{\Delta}$
D2	20	1	0	1$^{\Delta}$	0	1$^{\Delta}$
D3	20	1	1	5	0	4
C	20	2	0	0$^{\Delta}$	0	0$^{\Delta}$

Annotation: compared to Group D3, $^{\Delta}P<0.05$.

(P<0.05); The comparison of other adverse reactions between the four groups had no statistical significance (P>0.05) (See **Table 6**).

Discussion

Preemptive analgesia, which refers to using some protective measures to prevent the occurrence of sensitization in central nervous system before the body hurt by Noxious stimulus, and relieve postoperative pain completely or partially [4]. Currently, drugs used mostly for preemptive analgesia are morphine, fentanyl and other opioids, these drugs have achieved certain results in various degrees [3, 12].

Dezocine is a new opioid analgesic, belonging to synthetic mixed opioid receptor agonist -antagonist [12, 13], mainly excite k receptors; compared with μ receptor -dependent, it has less typical complications like nausea and vomiting etc. and not easy to produce deliriumand anxiety [14]. And compared with morphine, the onset time, analgesic strength and time-effect etc. of dezocine are not weak [15]. But after Dezocine reaches a certain amount, increasing dose will not enhance the analgesic effect, but increase the incidence of side effects [8]. Dezocine is massively used in controlling surgical or trauma-related acute pain in clinical [13], however, the researches of its use in preemptive analgesia and the best dosage are rare.

Liu Ping et al. [16] found the application of Dezocine in gynecological laparoscopic operation can effectively relieve postoperative incisional pain, and reduce the use of analgesic drugs after operation. The results of this study showed, injection of different doses of Dezocine before anesthesia induction can achieve certain analgesic and sedative effect after Pelvic fixation surgery and can reduce stress response to surgery, which is consistent with the findings of Liu Ping et al. [22]. Dezocine dosage of 0.15 mg/kg (D2 group) has a more appropriate analgesic effect. Although the dosage of 0.1 mg/kg (D1 group) has some analgesic effect, as shown in **Tables 1**, **3**, the VAS scores and PCIA sufentanil consumption in group D1 are still significantly higher than that of group D2 and D3.

Hyperglycemia is an important feature of stress response in trauma and surgery [17, 18], and serum CRP level is positively correlated with surgical injury degree and postoperative stress reaction [11, 19, 20]. TNF-α and IL-6, as inflammatory factors, can aggravate postoperative injury, and its concentration in serum could be regarded as an objective index of surgical stress degree [21]. As shown in **Figure 1**, fluctuations of peri-operative BG concentration, C reactive protein (CRP), IL-6 and TNF-α in group D1, D2 and D3 are less than that of group C, with group D2 and D3 even smaller; It indicated that the use of dezocine in pelvic fixation for preemptive analgesia can effectively reduce the stress response, which is consistent with the findings of Hao Lina et al. [23] that preemptive analgesia of dezocine can effectively reduce postoperative inflammation and stress response to the total hip arthroplasty.

As shown in **Tables 4** and **5**, recovery time and extubation time of group D3 was longer than that of group D1, D2, and C; sedation scores after 2 postoperative hours of group D3 were higher than that of group D1, D2, and C; also the incidence of dizziness and drowsiness of group D3 was higher than those of the other three groups; all of these indicated that after 3-4 hours of metabolism in vivo, the dezocine injected before anesthesia induction (0.2 mg/kg) still had high blood drug concentration in vivo that resulted in the phenomenon of excessive sedation, this may be related with the long time to achieve effective blood drug concentration of dezocine and its long terminal half-life

[13]. So, appropriate dose of dezocine should be used for preemptive analgesia.

In summary, injection of dezocine (0.15 mg/kg and 0.2 mg/kg) 15 minutes before anesthesia induction in pelvic surgery for preemptive analgesia, can significantly reduce the postoperative pain and postoperative sufentanil consumption, as well as effectively inhibit the postoperative stress response. However, the dosage of 0.2 mg/kg is more likely result in excessive sedation; and 0.15 mg/kg is the appropriate dosage to reach the effect of analgesia and sedation.

Disclosure of conflict of interest

None.

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