Fentanyl and Dezocine Associated Application Enhance the Analgesic Effect in Female Patients: A Randomized, Double-blinded, Prospective, Control Study

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Abstract: To evaluate the analgesia effect and side effects of dezocine and fentanyl associated application in female patients, two hundred and forty female patients, American Society of Anesthesiologists (ASA) I～II, aged 18～45 years, weight 50～70 kg, scheduled for elective gynecological operation were studied. These patients were randomly divided into four groups, according to the equivalent and isometric method, the patients in group A received dezocine 0.11 mg/kg, group B received fentanyl 1.1 μg/kg, group C received dezocine 0.055 mg/kg, fentanyl 0.55 μg/kg, and group D received fentanyl 0.55 μg/kg, dezocine 0.055 mg/kg. Group C and group D are just the administration sequence difference. The pain threshold which was represented by mA were produced by the current stimulator, it was measured and recorded before the administration of opioid analgesics and 5 min, 15 min after opioid analgesics injection and the side effects were also recorded in 30 minutes after the treatment. The pain threshold in group C and D was significantly higher than that in group A and B ($P < 0.05$) at 5 min and 15 min,the incidence of side effects in group C was lower than that in group A, B and D in sleepiness, nausea, vomiting, pruritis and chest tightness ($P < 0.05$). So fentanyl and dezocine associated application has a better analgesic effect and less side effects than fentanyl or dezocine alone.

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1. Introduction

Opioid is main perioperative analgesic agents at present. Fentanyl, one of opioids, is widely used due to its good analgesia, short duration of action, but the side effects, such as nausea, vomiting, pruritis, and chest vigidity may impede its application. Although the side effects of fentanyl are not severe in some patients, the side effects which influenced its analgesia should not be ignored. Some experiments have demonstrated that the use of a low-dose opioid receptor antagonist or partial agonist combined with opioid will not only enhance the analgesic effects but also reduce a number of undesirable side effects (Stein,1991)(Gan et al,1997). Ko MCs experiments have demonstrated that activation of κ-opioid receptors attenuates morphine-induced scratching without interfering with antinociception in monkeys. This mechanism-based finding provides functional evidence in support of the clinical potential of κ-opioid receptors agonists as antipruritics in the presence of μ-opioid receptors agonist-induced pruritus(Ko et al,2003). Obara I found that κ-opioid receptor agonists can reduced the inflammatory edema significantly(Obara et al,2009). Dezocine is a full agonist of κ-receptor and partial agonist of μ-receptor without classic μ-receptor dependence. In addition, dezocine antagonizes the addiction of the opioid, including reversing the morphine addiction, improving harmful reflection, and the body stiff. The effect of dezocine on fentanly-induced analgesia and side effects have been still unknown at present, we designed this randomized, double-blinded, prospective, control study to investigate the effect of fentanyl and dezocine associated application in female patients preoperative.

2. Methods

Ethical approval for this study was provided by the Ethical Committee of the First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China. Written informed consent was obtained from all female patients enrolled before commencement of the study. 240 ASA class I～II female patients (aged 18～45 years, weight 50～70 kg) scheduled for elective gynecological operations were enrolled in this study. Exclusive criteria included known a history of smoking, alcoholism, cardiovascular diseases, hepatic and renal dysfunction, diabetes, chronic pain history, narcotic drug dependence and recent history of opioid application.

Patients enrolled in the study were assigned to four groups with 60 patients in each according to a computer-generated table.

Upon arrival at the operating room, all patients were cannulated with an intravenous (IV) cannula (22G) on the dorsum of the right forearm. Monitoring of each patient was accomplished by electrocardiogram, non-invasive blood pressure, pulse oximetry (SpO_2).

All patients accepted the percutaneous electrical stimulation from a current stimulator (Photoelectricity Ltd, Tokyo, Japan, type:MEB-5100) to make the patients become familiar with the procedure and distinguish accurately the pain threshold and tolerance threshold.The current stimulator delivered a square-wave current at a frequency of 50 Hz. Two electrodes, with a surface area of 1 cm^2, were placed 1.5 cm apart on the deltoid muscle of the right forearm. The intensity of the current delivered via the electrodes was increased stepwise from 0 mA by 0.2 mA. After each stimulation, the patient was asked if she started to feel pain. When the patient started to feel pain, the stimulus intensity was recorded as pain threshold. The pain threshold was each determined three times and the mean of three values was calculated(Nielsen et al,2007)(Brennum et al,1992)(Wunderlich et al,2011) .

Two hundred and forty female patients were randomly assigned to four groups. It is well known that the analgesic effect of dezocine is equipotent to morphine, and the analgesic effect of fentanyl is one hundred times stronger than that of morphine, so, the analgesic effcct of fentanyl is one hundred times of dezocine. According to the method, we used a standardized analgesic dose of fentanyl , the dose of other groups was on the basis of the dose of fentanyl to conduct an equivalent and isometric conversion, the patients in group A received dezocine 0. 11 mg/kg, group B received fentanyl 1.1 μg/kg, group C received dezocine 0.055 mg/kg,fentanyl 0.55 μg/kg, group D received fentanyl 0.55 μg/kg,dezocine 0.055 mg/kg. Dezocine 0. 11 mg/kg in group A is equipotent to fentanly 1.1 μg/kg in group B. Dezocine 0.055 mg/kg is equipotent to fentanyl 0.55 μg/kg, and Dezocine 0. 11 mg/kg or fentanly 1.1 μg/kg is equipotent to dezocine 0.055 mg/kg,fentanyl 0.55 μg/kg. Group C and group D are just the intravenous sequence difference. All drugs were provided by the hospital pharmacy (dezocine: SN10042021; Yangtze River Pharmaceutical, Co., Jiangsun, China; fentanyl: SN100302 Yichang Humanwell Pharmaceutical Co., Hubei, China), identical, and administered intravenously.

A blinded observer, who had not known of the premedication given to the patients, recorded the pain threshold before the administration of drugs (T0), 5 min (T1), and 15 min (T2) after injection. The side effects, sleepiness, nausea, vomiting, pruritis, and chest vigidity were also recorded in 30 minutes after the opioid analgesics injection. Oxygen was applied by facemask if desaturation was observed (SpO2 < 90%).

The measurement data were expressed as mean ± SD. The comparison of patient characteristics among four groups was performed by using one-way analysis of variance (ANOVA). The comparison of pain threshold among four groups was performed by using general linear model repeated-measures analyses or ANOVA. Pearson Chi-Square and Fisher's Exact Test were used to evaluate the significant difference of side effects. The software package SPSS ver.15.0 (SPSS Inc., Chicago, I11, USA) program was used for all analyses. A value of $P < 0.05$ was considered significant.

3. Results

The demographic profile age and weight were compared in Table 1. There was no significant difference among the four groups (Table 1).

Table 1 Patient characteristics

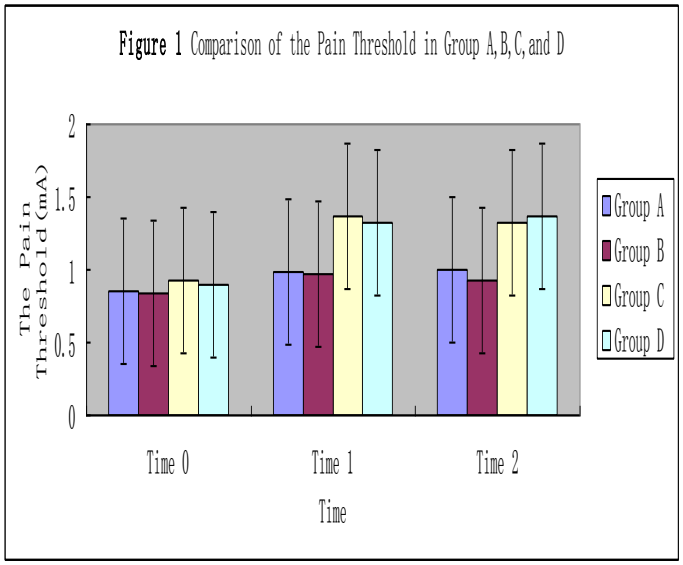
Patient characteristics	Group A (n = 60)	Group B (n = 60)	Group C (n = 60)	Group D (n = 60)	P value
age (years)	34. 8±6.8	36±6. 1	36±5. 5	34. 8±5. 0	0.49
weight (kg)	58. 2±6.3	58. 7±6. 9	56. 5±5. 8	56. 6±5. 1	0.10

Values are mean ± SD. No statistical difference was observed between the four groups.

The pain threshold was showed in Table 2, there was no significant difference at T0 among four groups ($P = 0.248$). The pain threshold in group C was significantly higher than that in group A and group B ($P = 0.00$ and $P = 0.00$) at T1 and T2, group D was significantly higher than that in group A and group B ($P = 0.00$ and $P = 0.00$) at T1 and T2. There was no significant difference between group A and group B ($P = 1.0$), it was the same between group C and group D ($P = 1.0$) (Table 2) (Figure 1).

Table 2 Changes in the pain threshold after treatment in four groups

Group	n	T0	T1	T2	
Group A	60	0.86±0.13	0.98±0.14	1.00±0.16	F_{time}=181.24 P = 0.
Group B	60	0.84±0.27	0.97±0.21	0.93±0.21	000
Group C	60	0.93±0.29	1.37±0.32	1.32±0.36	F_{group}=22.98 P = 0.
Group D	60	0.89±0.27	1.32±0.37	1.37±0.49	000



The four groups side effects were shown in Table 3.The group C had lower incidence than group A, B and D in sleepiness, nausea and vomiting, pruritis, and chest vigidity (P = 0. 000, P = 0. 008, P = 0. 03 and P = 0. 017). There was no significant difference among group A, B and D (Table 3). None of the patients suffered from hypoxemia (SpO2 < 90%), apnea.

Table 3 Incidence of the side effects in four groups

	GroupA (n = 60)	GroupB (n =60)	Group C (n = 60)	Group D (n = 60)	P value
sleepiness	30	32	11*	35	0.000
nausea,vomiting	24	30	15*	32	0.008
pruritis	5	8	0*	8	0.03
chest tightness	7	9	1*	12	0.017

4. Discussion

Did the analgesic effect of fentanyl and dezocine associated application enhance in female patients? In our study, we found that the analgesic effect of dezocine and fentanyl associated application increased obviously. The analgesic effect was evaluated by the pain threshold, the pain threshold was a current strength and the degree of pain which produced by multi-peak electrical stimulation. Although various experimental models were used to identify pain, the multi-peak electrical stimulation is the ideal method because of its fast beginning and stop, stability and reliability(Schafer et al,2000).Using current strength to reflect the pain is more accurate and objective than other methods of evaluating pain. So, in our study, we used the multi-peak electrical stimulation to assess the pain, and choose the right forearm deltoid muscle of all the patients to stimulate for uniform standard. Many factors have been associated with the pain threshold, such as age and sex(Enggaard et al,2001)(Edwards and Fillingim,2001) . In order to eliminate the differences of age and sex, we choose all the patients who were 18～45 years old female.

Crain SM and Shen KF reported opioid receptor had two-way role model, antagonist analgesia and analgesia, low-dose antagonist agent of the opioid receptor not only did not deteriorate the analgesic efficiency of opioid agonists but also enhanced, Ken-Fei Shen also reported low doses of opioid receptor antagonists may increase the antinociceptive potency and decrease the tolerance liability by co-administered morphine, codeine, or other modally-acting opioid

analgesics(Crain and Shen,2000). In our study, after opioid analgesic agents were given, the pain threshold of the four groups increased, but the group C and group D increased obviously, and their analgesic effect was better than group A or group B. In a previous study, opioid receptor antagonists or partial agonists reduced morphine-induced pruritus and nausea without reversal of the analgesic effect(Choi et al,2000). In our patients, we also found that group C had lower incidence of side effects than group A, B and D, such as sleepiness (11 vs 30, 32, 35), nausea and vomiting (15 vs 24, 30, 32), pruritis (0 vs 5, 8, 8), chest tightness (1 vs 7, 9, 12). The intravenous sequence of dezocine and fentanyl influenced the incidence of side effects(Sun et al,2011). In our study, we found that iv fentanyl before dezocine had higher incidence of side effects than iv dezocine before fentanyl. The mechanism(s) underlying these order-specific effects was not clear, it was tempting to speculate that this was not a single receptor effect, but was either a pharmacokinetic effect or due to effects on multiple receptors. A number of techniques have been applied to reduce the incidence of opioid-induced side effects, including the use of dexamethasone(Wang et al,1999), naloxone(Chio et al,1999), and droperidol, fentanyl concentration, propofol. Although the use of these drugs in earlier studies was able to prevent the side effects of opioid drugs, some of them are very limited in their clinical application. For example, dexamethasone is steroids and should be used under strict conditions, excessive dose naloxone can antagonize the analgesic effect of opioid drugs, droperidol is easy to cause extrapyramidal reactions(Kaufmann et al,1994). Other clinical research suggested that dilution of the fentanyl could not achieve the ideal analgesic effect in some patients. In a study, the incidence of opioid-related side effects was significantly low in patients received fentanyl in combination with propofol(Ramires-Ruiz et al,1995), but an overdose of propofol may cause fluctuation of hemodynamics. In our study, the associated complication of dezocine 0.055 mg/kg and fentanyl 0.55 μg/kg had not only enhanced the analgesic effect but also reduced the incidence of side effects. Consequently, we infer the analgesic effect of dezocine and fentanyl associated application is more than twice that of dezocine or fentanyl alone. So, dezocine and fentanyl associated application may be appropriate as an effective analgesic method.

In order to verify the efficacy of dezocine and fentanyl associated application in enhancing the analgesic effect and reducing side effects, we used dezocine and fentanly on those patients who needed the patient-controlled intrathecal analgesia (PCIA) and conducted postoperative follow-up. According to postoperative pain score and side effects, we found dezocine and fentanly associated application had a better analgesic effect and less side effects than fentanly alone in PCIA.

Dezocine is a new bridge central amino tetralin, a mixed opioid agonist/antagonist analgesic. Because various countries'drugs admittance system, dezocine may not be accessed in some country and available for use in all hospitals. However, dezocine is widely applied as a pain analgesic agent in many countries. A study clearly showed chronic naltrexone-induced up-regulation of opioid μ- and δ-receptors, while κ-receptor expression was enhanced in cortical but not in noncortical regions(Lesscher et al,2003). The result of clinical and animal experiments have demonstrated that the use of low-dose opioid receptor antagonists or partial agonists and opioid associated application will enhance the analgesic effect, meanwhile, antagonize some of undesirable side effects, such as nausea and pruritus. This double sword effect may due to the opioid receptors agonized and antagonized.

In our research, dezocine and fentanyl associated application has more powerful analgesic effect and less side effects than three the other groups, we infer that the possible mechanisms could be as follows: (1) Dezocine can make opioid peptides release, or replace the opioid peptides in the positions which have nothing to do with analgesia and make opioid peptides release, consequently, enhance the analgesic effect(Stein,1991). (2) Opioid receptors have two-way role model- excitatory opioid receptor and inhibitory opioid receptor, the former coupling Gs protein mediates hypersensitivity pain, nausea, vomiting, the latter coupling Gi/Go protein mediates analgesia. Low-dose opioid receptor antagonist or partial receptor agonist can specifically block Gs protein coupling excited effects but not block Gi/Gs protein coupling inhibiting effects. (3) Low-dose opioid receptor antagonist or partial receptor agonist can raise the density of opioid receptor and increase the activity, it is one of the mechanisms which don't antagonist but enhance the analgesic efficiency of opioid(Lesscher et al,2003). (4) Opioid agonists produce excitability for Ca^{2+} channel to make the density of Ca^{2+} in cells increased or Ca^{2+} channel open(Nakae et al,2003). A previous study has demonstrated low-dose opioid receptor antagonist or partial receptor agonist enhance the analgesic effect by Ca^{2+} and calcium channel.

In conclusion, our study indicates that dezocine and fentanyl associated application can not only enhance analgesic effect but also reduce the incidence of side effects. It is an effective and feasible method for clinical analgesia.

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