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Original Article

Postoperative intravenous analgesia with fentanyl alone or fentanyl in combination with naloxone, ketamine or dexmedetomidine in elderly patients

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Abstract: Objective: To compare the analgesic effects of fentanyl in combination with low-dose naloxone, ketamine, or dexmedetomidine, respectively, and fentanyl alone for postoperative intravenous analgesia in elderly patients. Methods: A total of 200 patients who needed intravenous patient-controlled analgesia (PCA) after surgery were enrolled in this study and divided into four groups based on a random number table: fentanyl group (F group, n=50), fentanyl + ketamine group (FK group, n=50), fentanyl + naloxone group (FN group, n=50), and fentanyl + dexmedetomidine (FD group, n=50). The time to first PCA after operation, overall frequency of PCA, overall doses of fentanyl in the first post-operative 24 h, pain intensity at different time points, changes in hemodynamics, incidences of postoperative complications and patients' satisfaction were compared among the four groups. Results: The visual analogue scale (VAS) scores at 6 h, 12 h, 24 h postoperatively were basically similar among the patients in the four groups and the differences had no statistical significance (all P>0.05). As compared with the patients in the F group, those in the rest groups had apparently lower doses of fentanyl in the first 24 h after operation, longer time to first PCA and reduced overall frequency of PCA (all P<0.05). Differences in mean artery pressure (MAP) at 2 h, 6 h and 12 h were not significant among the patients in the four groups (all P>0.05). The heart rate (HR) after operation differed insignificantly from that of before operation in the FD group (P>0.05), but HR was significantly higher than those before operation in the rest three groups, and all higher than that in the FD group (all P<0.05). In comparison with FK and F groups, the numbers of patients presenting nausea, vomiting and pruritus obviously reduced in both the FD and FN group (all P<0.05), while patients' satisfaction were improved (both P<0.05). No sign of bradycardia, hypotension, oversedation or respiratory restrictions was found in each group. Conclusion: As compared with fentanyl alone, fentanyl combined with naloxone, ketamine or dexmedetomidine for intravenous PCA after operation is associated with lower-dose fentanyl, fewer side effects and improved satisfaction with PCA in patients.

Keywords: Fentanyl, naloxone, ketamine, dexmedetomidine, intravenous analgesia

Introduction

A majority of elderly patients have coexisting conditions involving the heart, the lung and the brain [1]. That's why after operation or trauma, these patients have poor stress response to pain and trauma, and their rates of cardiovascular and cerebrovascular adverse events are higher [2]. Meanwhile, the pain causes reduced postoperative cough strength and sputum output in elderly patients, leading to increased risk for infection in the respiratory tract and the declined compliance of lungs [3]. Therefore, postoperative analgesia is necessary for them. However, fentanyl alone for intravenous analgesia might lead to incomplete analgesia, too high single or overall doses, or other adverse events like vomiting, nausea or local skin pruritus [4, 5]. Especially, the delayed respiratory restrictions may lead to higher risk for hypoxemia and hypercapnia. Therefore, postoperative analgesia should be administered judiciously in the elderly patients [6-8].

Naloxone is a μ-opioid receptor antagonist. Low-dose naloxone has been found to alleviate the adverse reactions caused by opioids and improve the analgesic effect of opioids [9].

Ketamine, a kind of NDMA receptor narcotic analgesics, can also act directly on opioid receptors, with higher dose producing stronger analgesic and sedative effects [10]. Dexmedetomidine, a highly selective and effective alpha 2-adrenergic receptor agonist, has the functions of analgesia, sedation, suppression of sympathetic nerves and anti-anxiety, but without obvious respiratory restrictions [11]. Nevertheless, it hasn't been reported the efficacy of fentanyl alone versus fentanyl plus low-dose ketamine, naloxone or dexmedetomidine for postoperative intravenous patient-controlled analgesia (PCA) in elderly patients.

In this study, we selected 200 patients in need of intravenous patient-controlled analgesia (PCA) from April 2014 to April 2017 in our hospital, and compared the analgesic effect of four different regimens for postoperative intravenous analgesia in the elderly patients: fentanyl combined with low-dose naloxone, ketamine or dexmedetomidine, and fentanyl alone.

Materials and methods

Patients

This study was reviewed and approved by the Ethics Committee of our hospital, and written informed consent was obtained from all patients and their families. A total of 200 patients who received PCA after surgery were enrolled and divided into four groups according to a random number table: F group (fentanyl group, n=50), fentanyl + ketamine group (FK group, n=50), fentanyl + naloxone group (FN group, n=50), and fentanyl + dexmedetomidine (FD group, n=50).

Inclusion criteria: Elderly patients with American Society of Anesthesiologists (ASA) of Class I or II, had operations under general anesthesia; needed PCA after operation; provided written informed consent form voluntarily or were able to assist with completion of relative examinations.

Exclusion criteria: Patients had severe underlying diseases including heart disease, uremia, coagulation disorder and so forth, mental disease, were intolerant to analgesic agents, didn't cooperate resolutely, or had bradycardia or respiratory restrictions.

Group assignment

F group, fentanyl at 0.4 μg/kg/h; FN group, fentanyl at 0.4 μg/kg/h + naloxone at 60 μg/kg/h; FK group, fentanyl at 0.4 μg/kg /h plus ketamine at 70 μg/kg/h; FD group, fentanyl at 0.4 μg/kg/h plus dexmedetomidine at 0.2 μg/kg/h. All the patients in the four groups were given intravenous PCA (2 ml/h) immediately after sobriety from general anesthesia, with a 0.5 ml bolus dose and a 15 min lock-time.

This study was double-blinded. Namely, the medical staff were unaware of the protocol examined and recorded pain and other relevant conditions of the patients who were also unaware of the protocol in the first 24 h after operation.

Follow-up and outcome measures

Relevant outcomes among the patients in the four groups were assessed, including time to first PCA, VAS scores, overall frequency of PCA, total dosage of fentanyl in the first 24 h (additional use when VAS scores ≥4, dose: 0.005 mg/kg), pain and changes in hemodynamics at different time points, patients' satisfaction, rates of analgesia-related adverse events including postoperative nausea, vomiting, sinus bradycardia, too low blood pressure, oversedation and respiratory restrictions.

The VAS is a scale used to describe pain intensity with scores ranging from 0 to 10, with 0 indicating no pain and 10 extremely pain. Patients chose one of the ten numbers to describe their pain according to their own feeling, with 0 indicating no pain, <3 slight but tolerable pain, 4-6 comparatively pain influencing quality of sleep, but still tolerable, 7-10 intolerable, incremental severe pain influencing appetite and quality of sleep. At 6 h, 12 h and 24 h postoperatively, VAS scoring was conducted on patients.

On the first day after operation, the patients were investigated with regard to their postoperative satisfaction based on a self-made questionnaire. The main contents included the patients' discomfort during operation, postoperative analgesic effect, adverse reaction, recovery, etc. The questionnaire includes a total of 100 scores, with 81-100 indicating the patient is quite satisfied with the outcome of analgesic effect, 60-80 indicating the patient is

Table 1. General information of patients in four groups

Variable	Group F	FN group	FK group	FD group	F/χ^2	*P* value
Case	50	50	50	50		
Sex					0.805	0.848
Male	25	22	24	21		
Female	25	28	26	29		
Age (year)	58.3±11.1	59.6±14.3	60.4±10.8	58.6±12.9	0.085	0.926
Weight (kg)	65.2±12.3	63.8±19.5	63.7±24.2	64.1±22.3	0.151	0.863
Operation type (n)					3.928	0.985
Orthopaedics	16	13	13	17		
General surgery	13	12	11	14		
Urinary	11	16	15	12		
Gynaecology	5	5	7	4		
Others	5	4	4	3		
Operation time (min)	71.5±9.5	69.3±8.6	72.1±10.2	68.9±12.1	0.229	0.832
Fentanyl dose during anesthesia (mg)	0.132±0.042	0.135±0.023	0.141±0.035	0.143±0.026	0.390	0.711

Table 2. Comparison of VAS scores at postoperative 6 h, 12 h and 24 h in four groups

Variable	6 h	12 h	24 h
F group (n=50)	3.1±0.6	4.2±0.3	3.2±0.3
FN group (n=50)	3.4±0.7	3.9±0.5	2.9±0.2
FK group (n=50)	3.2±0.3	4.1±0.7	3.1±0.5
FD group (n=50)	2.9±0.5	4.0±0.8	3.0±0.8
F value	0.741	0.674	0.655
P value	0.342	0.298	0.256

Table 3. Comparison of drug-dose among four groups

Variable	24 h fentanyl dose (μg)	Frequency of PCA
F group (n=50)	589±23.3	65.2±12.3
FN group (n=50)	410±19.3*	41.8±15.5*
FK group (n=50)	395±26.1*	41.7±14.2*
FD group (n=50)	421±27.1*	43.1±12.3*
F value	0.026	0.054
P value	0.015	0.023

Note: Compared with F group, *P<0.05.

generally satisfied with the effect of ablation, <60 indicating the patient is dissatisfied with the effect of ablation. Patients' satisfaction = No. of cases of extreme satisfaction + No. of cases of satisfaction)/No. of total cases * 100%.

Statistical analysis

SPSS 17.0, the commonly used tool for statistical analysis, was adopted to collect and analyze the relevant data. Quantitative data were expressed as rates, and the differences among the four groups and two independent samples were compared by the chi-square test and the chi-square partition test. Measurement data were expressed as mean ± standard deviation and the univariate analysis of variance and the Bonferroni test were used to make comparisons among the four groups. The comparisons of data at multiple time points were conducted by repeated measures analysis of variance with Bonferroni post-hoc test. P<0.05 was deemed to be statistically significant.

Results

General information

A total of 200 patients who needed postoperative PCA were enrolled, with an age of 70-85 years and a weight of 42-105 kg. There were 50 cases in each group (F group, FN group, FK group, FD group). The differences in general information revealed no statistical significance (P>0.05, **Table 1**).

Comparison of curative effects of four groups

The VAS scores among the patients in the F group, the FN group, the FK group and the FD group at 6 h, 12 h, and 24 h postoperatively were not significantly different (P>0.05, **Table 2**).

Compared with F group, the doses of fentanyl in the first 24 h after operation were remarkably decreased among patients in the rest three

Table 4. Comparison of postoperative MAP and HR among four groups

Variable	F group (n=50)	FN group (n=50)	FK group (n=50)	FD group (n=50)
HR (time/min)				
Before operation	73.4±12.2	73.5±11.3	74.1±14.4	74.2±10.1
2 h after operation	96.5±11.1*,#	95.2±12.3*,#	96.1±13.2*,#	75.9±11.9
6 h after operation	90.5±13.2*,#	89.2±11.9*,#	89.9±10.0*,#	73.6±13.2
12 h after operation	87.5±11.8*,#	86.3±12.1*,#	86.7±12.3*,#	71.2±9.3
MAP (kPa)				
Before operation	12.6±1.3	12.8±1.9	12.7±0.9	12.8±0.8
2 h after operation	13.9±1.2	14.1±1.1	13.8±1.5	13.7±1.2
6 h after operation	12.5±1.5	12.9±1.3	12.7±0.8	12.5±1.2
12 h after operation	12.3±0.9	12.5±1.0	12.4±0.9	12.3±1.1

Note: Compared with the same group before operation, *P<0.05; compared with FD group at the same point, #P<0.05.

Table 5. Comparison of postoperative complications among patients in four groups

	F group (n=50)	FN group (n=50)	FK group (n=50)	FD group (n=50)	χ^2	*P* value
Nausea and vomiting	24	6*,#	23	2*,#	0.033	0.005
Pruritus	19	2*,#	17	1*,#	0.051	0.001
Bradycardia	0	0	0	0		
Hypotension	0	0	0	0		
Over sedation	0	0	0	0		
Respiratory restrictions	0	0	0	0		

Note: Compared with F group, *P<0.008 (0.05/6); compared with FK group, #P<0.008.

Table 6. Comparison of satisfaction with postoperative analgesia among the patients in four groups

	F group (n=50)	FN group (n=50)	FK group (n=50)	FD group (n=50)	χ^2	*P* value
Extreme satisfaction	16	26	20	35		
Satisfaction	9	12	13	19		
Dissatisfaction	20	5	19	6		
Satisfaction magnitude	55.6%	88.4%*,#	63.5%	90.0%*,#	14.603	0.011

Note: Compared with F group, *P<0.008; compared with FK group, #P<0.008.

groups (P=0.002, P=0.000, P=0.005 in the FN group, the FK group and the FD group, respectively), and the overall frequency of PCA were apparently reduced (P=0.012, P=0.011, P=0.020 in the FN group, the FK group and the FD group, respectively). See **Table 3**.

The mean arterial pressure (MAP) at 2 h, 6 h and 12 h were not significantly different among the patients in the four groups (all P>0.05). The heart rate (HR) after operation did not differ significantly from that before operation in the FD group (P>0.05), but the HR in the other groups were evidently increased, and higher than that in the FD group (all P<0.05, **Table 4**).

As compared with the FK group and the F Group, the incidences of nausea, vomiting and pruritus in the first 24 h were reduced substantially in the FD group and the FN group (P<0.05, **Table 5**), patients' satisfaction were significantly improved (P<0.05, **Table 6**). In all the groups, no sign of sinus bradycardia, hypotension, respiratory restrictions or oversedation was found (**Table 5**).

Discussion

In this study, it was revealed that low-dose naloxone (60 μg/kg/h), ketamine (70 μg/kg/h), dexmedetomidine (0.2 μg/kg/h) combined with fentanyl (0.4 μg/kg/h) respectively enhanced the effects of sedation and analgesia after operation, therefore relatively cut down the dosage of fentanyl and overall frequency of PCA.

Crain et al. reported in their study that naloxone realized analgesic action by mainly stimulating opioid receptor κ subtypes, and led to hyperalgesia by antagonizing μ-opioid [12]. Ketamine is a noncompetitive antagonist of N-methyl D-aspartic acid glutamic acid (NMDA) receptor. At the same time, NMDA receptor has a close relationship with patients' dependence and tolerance to opioids, so applying low-dose ketamine in the pain tolerable to opioids can result in a lasting and fast analgesic effect [13, 14]. Besides, in one study it was testified that ket-

amine could directly act on opioid receptor and exert its analgesic effect [15]. Nevertheless, dexmedotemidine may play a role in analgesia and sedation by inhibiting peripheral nerve C-fiber and Aδ-fiber or regulate hyperalgesia by activating α_{2A}-receptor, therefore synergizing with fentanyl to realize their analgesic effects [16, 17].

In the present study, as compared with fentanyl alone or fentanyl combined with low-dose ketamine, significantly lower rates of postoperative nausea, vomiting and pruritus and higher satisfaction could be obtained by jointly administering low-dose naloxone and dexmedetomidine. It was likely due to the use of naloxone and dexmedetomidine, which reduced the doses of analgesic opioids, thereby decreasing the rates of relevant complications and improving patients' satisfaction and comfort [18, 19]. Differences in VAS scores at 6 h, 12 h, and 24 h had no statistical significance among the four groups, indicating that postoperative pain were generally under control in the four groups. And vital signs of the four groups before and after surgery were all within normal range, with high safety. Unlike the other three groups, HR and other vital signs before surgery had no statistical differences from those after surgery among patients in the FD group. This may be attributed to potential sedative function of dexmedetomidine. Meanwhile, dexmedetomidine has been proved to cause arrhythmia [20]. Nevertheless, similar results were not noted in the present study. It might be due to the low-dose dexmedetomidine or the synergy of fentanyl and dexmedetomidine attenuating the side effect of bradycardia caused by dexmedetomidine.

The relatively inadequate follow-up time and small sample size may potentially lead to any bias in this study. In the future, prospective trials with a large enough sample size and longer follow-up time will be performed, so as to extensively promote mixing fentanyl with low-doses of ketamine or dexmedetomidine for postoperative analgesia in clinic practice.

In summary, the use of fentanyl combined with low-dose naloxone or dexmedetomidine for analgesia can better reduce the incidence of drug-related complications and receive higher satisfaction from patients, which is more effective than fentanyl alone or fentanyl combined with low-dose ketamine. Hence, it is worthy of further promotion in clinic practice.

Disclosure of conflict of interest

None.

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