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Appropriate method of administration of propofol, fentanyl, and ketamine for patient-controlled sedation and analgesia during extracorporeal shock-wave lithotripsy

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Abstract

Purpose. The aim of this study was to identify the appropriate method for administering propofol, fentanyl, and ketamine (PFK) for patient-controlled sedation and analgesia (PCSA) during extracorporeal shock-wave lithotripsy (ESWL).

Methods. Twenty-one unpremedicated patients were randomly assigned to three groups that received different drug administration regimens. (group 1: low loading dose and high demand bolus, group 2: high loading dose and demand bolus, group 3: high loading dose and low demand bolus).

Results. The patients in all groups were hemodynamically stable during ESWL. Oxygen desaturation was recognized in all groups, but was avoided by $2\,l \cdot min^{-1}$ of oxygen supply via a nasal prong. The total administration dose of the drugs was significantly higher ($P < 0.05$) in group 2 than in groups 1 and 3. The median level of sedation was the same, but the episodes of oversedation were not recognized in group 3 ($P < 0.05$). A significant difference in the frequency of episodes of oversedation was found between groups 2 and 3 ($P < 0.05$). The results were good or excellent for almost all patients, and were assessed as fair by only one patient in group 2.

Conclusion. We concluded that the method used for group 3 is the most appropriate for administering PFK for PCSA during ESWL.

Key words: Propofol, fentanyl, and ketamine (PFK); Patient-controlled sedation and analgesia (PCSA); Extracorporeal shock-wave lithotripsy (ESWL)

Introduction

Extracorporeal shock-wave lithotripsy (ESWL) for renal stones causes pain and discomfort in many patients. Today, various types of anesthesia are applied for ESWL, including general anesthesia [1], epidural anesthesia [1], local anesthesia [2,3], and intravenous injection of sedative-hypnotics with analgesics [4].

Recently, a technique called patient-controlled sedation and analgesia (PCSA) [5] has been developed. This technique is based on negative feedback technology in a closed-loop system according to the patient's own will. Theoretically, this method can allow patients to receive an appropriate level of sedation and analgesia.

Various combinations of PCSA drugs have also been considered. These include propofol with fentanyl [5] or alfentanil [6]; however, such drugs have an inherent inhibitory effect on hemodynamics [5] and respiration [6].

Ketamine is a sedative-analgesic that does not induce any clinically significant ventilatory depression and also has a positive hemodynamic effect [7]. Monk [7] reported that ketamine infusion provided superior intraoperative cardiorespiratory stability; however, it was also associated with more disruptive movements. Rosen [8] recommended low doses of ketamine with propofol for balanced sedation. We therefore tried a new combination of a low dose of ketamine with propofol and fentanyl for PCSA during ESWL.

A continuous infusion technique combined with demand boluses offers the benefit of a steady plasma concentration while maintaining patient comfort and the ability to rapidly adjust the plasma drug concentration as the level of stimulation changes [6]. The doses for the continuous infusion of propofol and fentanyl were determined on the basis of the findings of previous papers [5,6]. The dose for the continuous infusion of ketamine was determined by taking into account the relative infusion ratio of ketamine against propofol of total intravenous anesthesia [9,10]. Our preliminary data revealed that the continuous infusion of $0.20\,mg \cdot kg^{-1} \cdot h^{-1}$ of ketamine with $1\,mg \cdot kg^{-1} \cdot h^{-1}$ of propofol and $1\,\mu g \cdot kg^{-1} \cdot h^{-1}$ of fentanyl for 1 h allowed

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the patients to maintain consciousness (data not shown). The purpose of this study was to determine the appropriate method for administering these drugs for PCSA during ESWL, from the viewpoint of hemodynamics, respiration, consciousness, and patient satisfaction.

Materials and methods

Twenty-one unpremedicated adult patients, ASA physical status I and II, undergoing elective ESWL were studied. After approval of the local ethics committee and written informed consent had been obtained, the patients were randomly assigned to three groups. The planned drug administration regimen is listed in Table 1. The differences in the methods of drug administration between these three groups were the loading dose and additional self-administration. The loading dose of propofol was either 0.25 or 0.35 mg·kg^{-1}. The additional self-administered dose of propofol was either 0.25 or 0.20 mg·kg^{-1}. The maintenance dose and the lockout interval (3 min) were the same in the three groups. All three drugs were mixed and packed in a syringe. The drug mixing ratio of the solution was also the same in all three groups.

Preoperatively, arterial blood pressure (BP) and heart rate (HR) were determined by an automatic blood pressure cuff and an ECG, respectively, and the respiratory rate (RR) and room air oxygen saturation (SpO_2) were determined by a precordial stethoscope and pulse oximeter. After placement of the intravenous catheter, lidocaine 20 mg was administer to prevent any pain from the propofol injection. The drugs were administered by an infusion pump (Baxter APII, Deerfield, USA). The infusion was started 10 min before starting the shock-wave treatment and continued thereafter throughout the ESWL. The patient-controlled infusion device was available to the patient throughout the ESWL.

The cardiorespiratory variables (BP, HR, RR, and SpO_2) were recorded during the ESWL procedure. In response to oxygen desaturation ($SpO_2 < 90\%$), oxygen was supplied at 2 l·min^{-1} via a nasal prong. If oxygen desaturation started, the oxygen supply was continued until PCSA was completed.

The degree of sedation was assessed at 5-min intervals after the loading dose. The level of sedation was assessed by a five-point scale: 1 = fully awake; 2 = drowsy; 3 = eyes closed, but arousable by command; 4 = eyes closed, but arousable by mild physical stimulation; 5 = eyes closed and unarousable by mild physical stimulation [11]. Levels 4 and 5 were considered to be oversedation.

ESWL was performed with a Medstone lithotriptor (Model STS, Irvine, USA), which is a dry-type lithotriptor equipped with an X-ray and ultrasound localization system and a spark-gap generator [12]. All patients received 2400 shots of 24 kV (maximal voltage) shock waves.

After the procedure, the patient was asked to independently evaluate the adequacy of the sedation-analgesia technique according to a four-level scale: inadequate, fair, good, or excellent.

Statistical analysis was performed by one-way analysis of variance (ANOVA) with Fisher's exact test. Nominal data were analyzed by chi-square. The Kruskal-Wallis test and the Mann-Whitney U test were also used to compare the sedation scores among the three groups. Spearman's correlation coefficient by rank was used to test the correlation between the frequency of episodes of oversedation and other factors. Differences were considered to be statistically significant when the P value was <0.05. All values are expressed as means ± standard deviation.

Results

The demographics of the patients and the duration of the procedure were not significantly different in the three groups (Table 2).

Table 1. Administration regimen of propofol, fentanyl, and ketamine

Drug	Group	Loading dose (·kg^{-1})	Self administration (·kg^{-1})	Maintenance (·kg·h^{-1})
Propofol (mg)	1	0.25	0.25	1
	2	0.35	0.25	
	3	0.35	0.20	
Fentanyl (μg)	1	0.25	0.25	1
	2	0.35	0.25	
	3	0.35	0.20	
Ketamine (mg)	1	0.05	0.05	0.2
	2	0.07	0.05	
	3	0.07	0.04	

Table 2. Demographics of patients and duration of procedure

Group	Age (yr)[a]	Weight (kg)[a]	Sex (M:F)	ESWL time (min)[a]
1	55 ± 13	65 ± 15	5:2	51 ± 6
2	55 ± 8	65 ± 7	6:1	56 ± 15
3	52 ± 8	65 ± 14	4:3	51 ± 6

[a] Values are means ± SD

Table 3. PCSA data and sedation score

Group	PCSA bolus demands (n)[a]	Successful delivery (n)[a]	Total propofol dose ($mg \cdot kg^{-1}$)[a]	Total fentanyl dose ($\mu g \cdot kg^{-1}$)	Total ketamine dose ($mg \cdot kg^{-1}$)[a]	Sedation score (median)	Episodes of oversedation (%)
1	30 ± 41	3 ± 2	2.0 ± 0.7	2.0 ± 0.7	0.4 ± 0.1	3	29
2	18 ± 14	6 ± 2	3.2 ± 0.4[b]	3.2 ± 0.4[b]	0.6 ± 0.1[b]	3	57[c]
3	5 ± 10	3 ± 4	2.1 ± 0.8	2.1 ± 0.8	0.4 ± 0.2	3	0

[a] Values are means ± SD
[b] The total doses of the drugs used were significantly higher ($P < 0.05$) in group 2 than in groups 1 and 3
[c] The median level of sedation was the same, but the frequency of episodes of oversedation was significantly different (Kruskal-Wallis test, $P < 0.05$). The difference was in group 1 and 3 (Mann-Whitney U test, $P < 0.05$)

Table 4. Perioperative SpO_2 (%)[a]

Group	Pre-PCSA[a]	Lowest Desaturation (%) value[a]	($SaO_2 < 90\%$)	O_2 supply ($2 l \cdot min^{-1}$)[a]	Post-PCSA (5 min after)[a]
1	98 ± 1	87 ± 8	86	96 ± 2	96 ± 2
2	98 + 1	87 ± 4	100	95 ± 3	96 ± 2
3	97 + 1	90 ± 5	43	93 ± 6	96 ± 2

[a] Values are means ± SD

The total administered dose of the drugs was significantly higher ($P < 0.05$) in group 2 than in groups 1 and 3 (Table 3). The number of PCSA boluses demanded and the number of successful deliveries were not significantly different among the three groups. The patient-controlled technique was assessed on the basis of the successful demands (number of successful deliveries) against unsuccessful demands [(number of PCSA boluses demanded) − (number of successful deliveries)] [5,13,14]. In this study, the rates increased from group 1 (0.1) to group 2 (0.5) to group 3 (1.5).

The median level of sedation was the same, but no episodes of oversedation were recognized in group 3 ($P < 0.05$). There was a significant difference in the frequency of oversedation episodes between groups 2 and 3 ($P < 0.05$). The frequency of oversedation episodes correlated with the total administered dose of the drugs ($r = 0.57$, $P < 0.01$).

There was no significant difference in the frequency of occurrence of desaturation ($SpO_2 < 90\%$) in the three groups (Table 4). Oxygen supplied at a rate of $2 l \cdot min^{-1}$ via a nasal prong was effective for preventing desaturation (there was a significant difference between the lowest value of SpO_2 with room air and the lowest value of that with the oxygen supply; $P < 0.01$). As a result, no desaturation was recognized after the oxygen supply. At 5 min after stopping both PCSA and oxygen supply, the SpO_2 recovered completely ($P < 0.01$).

There was no significant difference in the frequency of occurrence of bradypnea ($RR < 10$) during PCSA in the three groups (Table 5). RR did not recover within 5 min after PCSA was stopped ($P < 0.05$), and it continued at a slightly lower level than pre-PCSA. Postoperative bradypnea persisted in one case each in groups 2 ($RR = 9$) and 3 ($RR = 8$).

The mean arterial blood pressure (MAP) was stable during the induction of PCSA (Table 6). The highest value of MAP in group 2 was higher than in group 3 ($P < 0.05$). HR was stable during the induction of PCSA. The frequency of bradycardia ($HR < 60 \cdot min^{-1}$) was not significantly different among the three groups (Table 7). Only one patient in group 1 experienced transient severe bradycardia ($HR\ 48 \cdot min^{-1}$). However, this disappeared before medication. At 5 min after PCSA was

Table 5. Perioperative respiratory rate

Group	Pre-PCSA[a]	Lowest value[a]	Bradypnea(%) (RR < 10)[a]	Post-PCSA (5 min after)[a]
1	17 ± 3	12 ± 2	0	15 ± 4
2	17 ± 3	11 ± 1	14	13 ± 3
3	17 ± 4	12 ± 3	29	15 ± 4

[a] Values are means ± SD

Table 6. Perioperative mean arterial blood pressure (mm Hg)[a]

Group	Preinduction	5 min after induction	10 min after induction	Lowest value	Highest value	Post-PCSA (5 min after)
1	104 ± 10	102 ± 12	101 ± 8	86 ± 7	115 ± 9	99 ± 7
2	107 ± 9	107 ± 8	106 ± 5	86 ± 14	118 ± 7[b]	105 ± 15
3	98 ± 8	101 ± 8	99 ± 8	91 ± 9	107 ± 4	101 ± 9

[a] All values are means ± SD
[b] The highest value of MAP of group 2 was higher than that of group 1 and 3 ($P < 0.05$)

Table 7. Perioperative heart rate (beats·min^{-1})

Group	Preinduction[a]	5 min after induction[a]	10 min after induction[a]	Lowest value[a]	Bradycardia (%)	Highest value[a]	Post-PCSA (5 min after)[a]
1	78 ± 25	76 ± 21	75 ± 19	64 ± 13	43	82 ± 23	67 ± 12
2	82 ± 11	84 ± 14	81 ± 16	64 ± 7	14	91 ± 13	74 ± 11
3	77 ± 17	71 ± 10	68 ± 8	62 ± 9	57	83 ± 10	64 ± 8

[a] Values are means ± SD

Table 8. Postoperative assesment of adequacy of PCSA by the patients (%)

Group	Excellent	Good	Fair	Inadequate
1	43	57	0	0
2	57	29	14	0
3	57	43	0	0

stopped, HR did not recover completely to pre-PCSA values ($P < 0.05$) and continued at a slightly lower value than pre-PCSA.

Almost all patients reported a good or excellent level of satisfaction, and only one patient in group 2 reported fair (Table 8). There was no significant difference in satisfaction among the groups. Twelve patients had past experiences of ESWL under epidural anesthesia. All of them commented that PCSA was better than epidural anesthesia. All patients said they would, if required, repeat the same procedure and technique using PCSA.

There was no case of any disruptive movements inhibiting the procedures or resulting in a lack of cooperation with the operator.

Discussion

The results of this study indicate that the most appropriate method for administering PFK for PCSA was that used in group 3, which had a high loading dose and a low patient demand bolus. The method used in group 3 had a low incidence of oversedation and desaturation and a good adaptation of the patient demand.

The combination of either fentanyl [15] and ketamine [16] with propofol reduces the levels of both hypnotic and anesthetic doses of propofol. Sufficient sedation is acquired with a smaller dose of propofol combined with fentanyl or ketamine than with the dose of singly administered propofol. Our results suggest that the combination of propofol, fentanyl, and ketamine (PFK) had a dose-sparing effect on sedation. The continuous-infusion technique prevents a sudden decrease in the plasma concentration of propofol. The difference in the frequency of episodes of oversedation among the groups could be caused by a slight difference in the administered doses. We suspect that these results must be due to both the dose-sparing effect of the combination of PFK and the stable plasma concentration of the drugs.

All groups achieved a light level of conscious sedation with eyes closed but were arousable by command. This level of sedation is considered to be both safe and effective, because it allows the patients to keep their airways open. On the other hand, oversedation is dangerous. We propose that the use of an appropriate loading dose and additional self-administration is essential to avoid oversedation.

Although oxygen desaturation could not be avoided in any group, it could be avoided by supplying oxygen at $2 l \cdot min^{-1}$ via a nasal prong. RR was reduced during PCSA, and slight bradypnea persisted in the postoperative period in some cases. However, the patients' consciousness was clear and there was no oxygen desaturation without an oxygen supply during the postoperative period.

The blood pressure was stable during PCSA in this study. Guit [9] reported that the combination of fentanyl with propofol depressed hemodynamics, but the combination of ketamine with propofol resulted in stable hemodynamics. The combination of PFK for total intravenous anesthesia (TIVA) achieves a stable hemodyamic level [10]. Our data suggest that the combination of low doses of PFK also has the same advantages as PFK anesthesia, which can achieve a stable level of hemodynamics.

Some patients in each group experienced bradycardia, but no patient needed medication, because the hemodynamics were stable and no arrhythmia was seen. Only one patient in group 1 experienced transient severe bradycardia with HR $48 \cdot min^{-1}$. A similar case was reported by Maroof [5], in which a patient had bradycardia with HR $38 \cdot min^{-1}$ and needed atropine. Mayer [17] reported that bradycardia with HR less than $40 \cdot min^{-1}$ was observed in more patients given fentanyl/propofol anesthesia than in those given ketamine/propofol anesthesia. We speculate that the ratio of ketamine to propofol and/or fentanyl in this study is low enough to inhibit the appearance of bradycardia.

Maroof [5] suggested that the positive psychological effect seen with PCSA is related to its good outcome. PCSA allows the patients to feel that they have some control over their pain and discomfort [5]. In this study, almost all patients had a good or excellent degree of satisfaction, but only one patient in group 2 assessed the results as fair. We suspect that the reason for this is a disturbance of the positive psychological effect of PCSA by an interruption of consciousness due to oversedation.

Our findings suggest that the most appropriate method of administering PFK for PCSA during ESWL is by giving a high loading dose in combination with a low patient-controlled demand bolus with continuous infusion.

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