Master of Medicine

Iatrogenic opioid withdrawal syndrome in critically ill patients: a retrospective cohort study

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Abstract

Background: Opioid withdrawal syndrome (OWS) may occur following the reduction or discontinuation of opioid analgesics. In critically ill pediatric patients, OWS is a common and clinically significant condition. As OSW in adult patients has not been assessed in detail, this study aimed to investigate the incidence, risk factors, and clinical features of OWS in patients treated in an adult intensive care unit (ICU).

Methods: This study was a retrospective evaluation of data from patients treated in the medical ICU for ≥ 3 days and who received only one type of opioid analgesic. OWS was assessed over a 24 hour period from discontinuation or reduction (by > 50%) of continuous opioid infusion. OWS was defined as the presence of ≥ 3 central nervous system or autonomic nervous system symptoms.

Results: In 126 patients treated with remifentanil (n = 58), fentanyl (n = 47), or morphine (n = 21), OWS was seen in 31.0%, 36.2%, and 9.5% of patients, respectively (p = 0.078). The most common symptom was a change in respiratory rate (remifentanil, 94.4%; fentanyl, 76.5%; morphine, 100%). Multivariate Cox-proportional hazards model showed that OWS

was associated with morphine treatment (hazard ratio: 0.17, 95% CI: 0.037–0.743) and duration of opioid infusion (hazard ratio: 0.566, 95% CI: 0.451–0.712).

Conclusions: No statistically significant difference in the incidence of OWS was observed among patients treated with different types of opioid analgesics, although a lower frequency was seen in patients receiving morphine. Prospective studies are required to confirm these preliminary results.

Keywords: Analgesics, intensive care unit, substance withdrawal syndrome, incidence

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Introduction

In mechanically ventilated critically ill patients, opioids are often required to manage pain and agitation [1]. When opioid therapy is abruptly discontinued, opioid withdrawal syndrome (OWS) can develop, indicated by the presence of neurologic symptoms such as anxiety, irritability, tachycardia, and tachypnea [2]. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines OWS as the occurrence of three or more characteristic symptoms (such as dysphoric mood, nausea, vomiting, diarrhea, or fever) within minutes to several days after cessation or reduction of high dose or prolonged opioid therapy [3]. However, it is difficult to apply these criteria in mechanically ventilated patients as symptom evaluation can be challenging.

Some OWS assessment tools have been validated for use in pediatric patients [4, 5], and the incidence of OWS in critically ill children has been reported to range between 10% and 57% [6, 7]. Several risk factors (such as cumulative dose, duration of analgesia, and the administration of sedative drugs) are known to increase the risk of OWS [8-11]. However, few studies have evaluated the incidence, symptoms, and risk factors for OWS in critically

ill adult patients [12, 13]. In addition, an assessment tool has not been established to evaluate the symptoms and diagnosis of OWS in this patient group. Although a prospective study recently reported an OWS incidence of 16.7% in adults, the study was limited by the use of the DSM-5 criteria to assess OWS and a lack of information on symptoms or type of opioid used [13].

The objective of the current study was to investigate the incidence of OWS in adult patients treated in a medical ICU. The clinical features and risk factors associated with OWS were also analyzed as a secondary objective.

Methods

Study design and population

This retrospective cohort study was conducted in the Asan Medical Center, Republic of Korea. Data from critically ill patients aged ≥ 18 years who were admitted to the medical ICU between November 2015 and October 2016 were evaluated. As of November 2016, the Health insurance review & assessment service of the Korea national government has prohibited the administration of remifentanil for more than 3 days; therefore, the period of enrollment was set to 1 year prior to this date. Patients were required to be supported on mechanical ventilation for > 3 days and to have received only one type of opioid. Patients were excluded if they suffered from central nervous system (CNS) diseases that disturbed the assessment of OWS or if they were discharged or died without reducing the opioid dose. The study protocol was approved by the Institutional Review Board of Asan Medical Center (IRB no. 2017-1248).

Opioid withdrawal syndrome

As there are no validated assessment tools for OWS in mechanically ventilated adult ICU patients, OWS assessment was based on several pediatric assessment tools and the DSM-5 criteria [4, 14]. OWS assessment was initiated following the cessation of opioid therapy or reduction by 50% of maximal dose, and continued for a maximum of 24 hours based on the context-sensitive half life of opioids [15-17]. If patients died or were transferred to the general ward, the evaluation could be terminated earlier than the defined period. If opioids were re-introduced or the dose increased 2-fold, OWS was evaluated from the initiation of assessment to the time of adjusted dosing. Also, in patients receiving a reduced opioid dose, if cessation occurred within 24 hours during the evaluation of OWS, the period of evaluation was prolonged to 24 hours from opioid cessation. Because OWS is known to occur more frequently as the cumulative duration of opioid administration increases in pediatric ICU patients, we only evaluated the last period in case of having many periods of assessment [7, 18, 19].

During the assessment period, five CNS symptoms were evaluated: 1. a change in the Confusion Assessment Method (CAM) scoring to a positive signal; 2. increased pupil size by

one plus signal; 3. Glasgow Coma Scale score increase of ≥ 2; 4. increased Richmond Agitation-Sedation Scale (RASS) score of ≥ 2; 5. new onset of seizures. In addition, six autonomic nervous system (ANS) symptoms were assessed: 1. new onset of fever or temperature increase of ≥ 1 ℃; 2 & 3. increased respiratory or pulse rate by 20% of the mean observed during the previous 4 hours; 4 & 5. increased frequency of suction at the endotracheal or oral secretion by more than twice the mean observed during the previous 4 hours; 6. new onset of loose stools or diarrhea. The starting time and duration of symptoms were also recorded. OWS was diagnosed if ≥ 3 of the symptoms persisted for 2 hours during the period of evaluation. Patients were excluded if other events occurred, such as extubation or the requirement for invasive procedures.

Data collection and clinical outcomes

The following demographic and clinical outcomes data were collected for each patient: age, sex, reason for ICU admission, comorbidities, history of opioid drugs used for more than 3 days, chronic alcoholism, septic shock or dialysis within 24 hours of admission to the

ICU, Sequential Organ Failure Assessment (SOFA) score at admission, and use of sedatives at the time of OWS evaluation. The reason for admission to the ICU was classified as infection, bleeding event, respiratory failure, heart failure, post-operative management, and others. Comorbidities comprised diabetes mellitus (DM), hypertension, respiratory disease, liver disease, renal disease, heart disease, solid cancer, hematologic malignancy, immunosuppression, and others. Clinical data included the duration and cumulative dose of opioid received prior to evaluation. All opioid doses were converted into morphine equivalents. For all enrolled patients, data on the occurrence of any of the 11 symptoms included in the assessment criteria, time of symptom onset, and the duration of symptoms were collected up to 24 hours after initiating the evaluation.

The primary outcome was the incidence of OWS according to the type of opioid administered. The clinical features of OWS were also analyzed as a secondary objective. Covariates, such as age, sex, and reason for ICU admission, were analyzed to evaluate risk factors for the development of OWS.

Statistical analysis

Descriptive data are expressed as proportions, and continuous variables as a median with interquartile range or mean plus standard deviation. The chi-square test or Fisher's exact test was used to compare categorical variables, while one-way analysis of variance or the Kruskal-Wallis test was used for comparing continuous variables with normal or non-normal distribution, which were corrected in post hoc analysis using Bonferroni's method. The multivariable Cox-proportional hazards model was used to identify independent predictors of OWS development. A final model was constructed using a stepwise method; *p*-values of 0.05 and 0.15 were set for entry and removal of variables. A two-sided p-value < 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows/Macintosh, Version 24.0 (IBM Corp., Armonk, NY).

Results

During the study period, 185 adult patients admitted to the medical ICU were screened; of these, 102 patients (55.1%) received remifentanil and 83 (44.9%) received other opioids (Figure 1). Of the 102 patients in the remifentanil group, 58 patients (56.9%) met the inclusion criteria. However, the inclusion period for patients receiving fentanyl or morphine was amended due to the limited number of eligible patients. Ultimately, 47 patients who had received fentanyl and 21 patients who had received morphine were included in the analysis. The main reasons for exclusion were administration of other opioids, no cessation or reduction of opioids, and the presence of a CNS comorbidity.

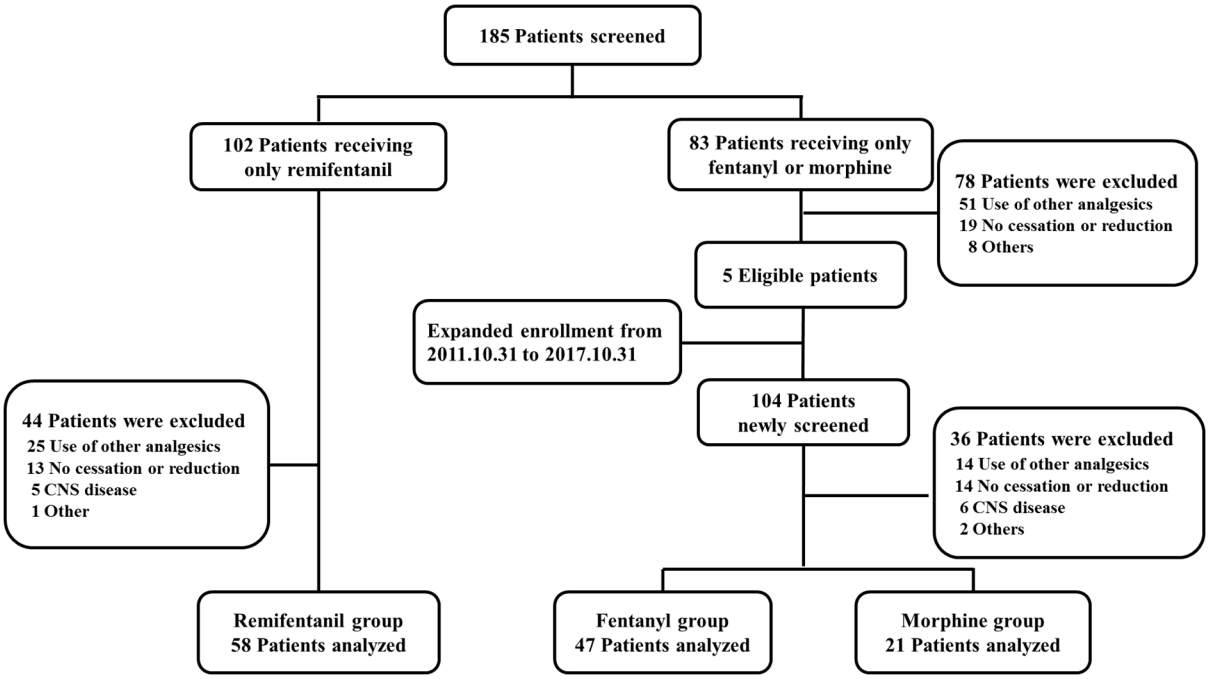

Fig. 1. The study population framework.

The baseline characteristics of the 126 patients included in the analysis are shown in Table 1. The mean patient age was 68.29 years (± 14.1 years), and 85% were male. The most common reasons for ICU admission were infection (48.4%) and respiratory failure (36.5%). The study patients had high severity of illness with mean SOFA scores of 9.95 (± 3.7). Comparison of the demographic variables according to type of opioid showed no significant differences in age, sex, reason for ICU admission, comorbidity, chronic alcoholism, septic shock, and dialysis. Statistically significant differences in the history of opioid exposure and SOFA score were seen between the groups; the remifentanil group had a slightly lower proportion of patients with a history of opioid exposure than other groups (p = 0.007), and patients in the fentanyl group had a higher level of disease severity than those in the morphine group (p = 0.004). There was a tendency for a higher use of sedatives in the remifentanil group than in other groups (p = 0.011); most of the remifentanil group (62.1%) had received a sedative in the assessment period, because there were a higher proportion of patients in this group undergoing de-escalation than in the other groups. Propofol was the most commonly used sedative in all three groups.

Table 1. Patient characteristics

Characteristics	All (n = 126)	Remifentanil (n = 58)	Fentanyl (n = 47)	Morphine (n = 21)
Median age, years	68.3 ± 14.1	71.1 ± 12.9	67.3 ± 16.1	62.7 ± 11.1
Male/female	85/41 (67.5/32.5)	42/16 (72.4/27.6)	29/18 (61.7/38.3)	14/7 (66.7/33.3)
Reason for ICU admission				
Infection	61 (48.4)	30 (51.7)	25 (53.2)	6 (28.6)
Bleeding event	8 (6.3)	3 (5.2)	4 (8.5)	1 (4.8)
Respiratory failure	46 (36.5)	20 (34.5)	14 (29.8)	12 (57.1)
Heart failure	5 (4.0)	3 (5.2)	1 (2.1)	1 (4.8)
Post-operation	4 (3.2)	2 (3.4)	2 (4.3)	0 (0.0)
Others	3 (2.4)	0 (0.0)	2 (4.3)	1 (4.8)
Comorbidity				
Diabetes mellitus	16 (12.7)	8 (13.8)	6 (12.8)	2 (9.5)
Hypertension	11 (8.7)	5 (8.6)	4 (8.5)	2 (9.5)
Respiratory disease	23 (18.3)	12 (20.7)	8 (17.0)	3 (14.3)
Liver disease	10 (7.9)	2 (3.4)	6 (12.8)	2 (9.5)
Renal disease	5 (4.0)	1 (1.7)	2 (4.3)	2 (9.5)
Cardiac disease	14 (11.1)	7 (12.1)	7 (14.9)	0 (0.0)
Solid cancer	25 (19.8)	11 (19.0)	10 (21.3)	4 (19.0)
Hematologic cancer	17 (13.5)	11 (19.0)	2 (4.3)	4 (19.0)
Immunosuppression	3 (2.4)	0 (0.0)	3 (6.4)	0 (0.0)
Others	14 (11.1)	7 (12.1)	4 (8.5)	3 (14.3)
History of opioid exposure*	22 (17.5)	4 (6.9)	14 (29.8)	4 (19.0)
Chronic alcoholics	13 (10.3)	4 (6.9)	7 (14.9)	2 (9.5)
Septic shock	45 (35.7)	17 (29.3)	23 (48.9)	5 (23.8)
SOFA score*	10.0 ± 3.7	9.7 ± 3.7	11.2 ± 3.4	8.0 ± 3.5[†]

Table 1. Continue

Dialysis	28 (22.2)	9 (15.5)	15 (31.9)	4 (19.0)
Sedatives				
No sedative*	65 (51.6)	22 (37.9)	28 (59.6)	15 (71.4)
Propofol*	43 (34.1)	33 (56.9)	8 (17.0)	2 (9.5)
Midazolam	5 (4.0)	2 (3.4)	2 (4.3)	1 (4.8)
Ketamine	8 (6.3)	2 (3.4)	4 (8.5)	2 (9.5)
Dexmedetomidine*	7 (5.6)	0 (0)	5 (8.5)	2 (9.5)

Results are reported as n (%) or mean ± SD. * Statistical significance when comparing the variables of the three groups. † vs. the fentanyl group. SOFA, Sequential Organ Failure Assessment.

The overall incidence of OWS was 29.4% (37 of 126 patients), with 18 patients (31.0%) in the remifentanil group, 17 (36.2%) in the fentanyl group, and two (9.5%) in the morphine group (Table 2). Although fewer patients in the morphine group developed OWS, there were no statistically significant differences between the three groups (p = 0.078). The type of withdrawal differed significantly between the remifentanil group and the other groups (p = 0.001). However, there was no difference in the incidence of OWS according to the type of withdrawal among the three groups. The total cumulative opioid dose (adjusted into the corresponding morphine dose) was highest in the remifentanil group (median, 5023.8 mg), compared with the fentanyl (median, 2090.4 mg) and morphine (median, 216.0 mg) groups. The total duration of opioid infusion did not differ between the three groups. The most common symptoms in all patients was a change in respiratory or pulse rate. Of the ANS symptoms, the onset of new fever was the least frequent. Of the CNS symptoms, a change in CAM, RASS, and pupil size occurred with similar frequency, but a change of Glasgow Coma Score or new onset seizure was less

common.

In the remifentanil group, a change in respiratory rate had the highest sensitivity for OWS (94.4%) of the 11 symptoms, but specificity was low (32.5%). By contrast, a change of RASS score (90.0%), increased oral secretion (95.0%), sputum (95.0%), and new onset loose stool or diarrhea (85.0%) showed high levels of specificity. Although the sensitivity of both a change of respiratory rate and pulse rate was lower, almost all patients with increased oral secretion (93.3%) or sputum (100.0%) satisfied the criteria for OWS in the fentanyl group. In the morphine group, there were too few patients to perform this analysis.

Table 2. Opioid withdrawal syndrome according to type of opioid analgesic

	Remifentanil (n = 58)	Fentanyl (n = 47)	Morphine (n = 21)	*p*-value
Opioid withdrawal syndrome	18 (31.0)	17 (36.2)	2 (9.5)	0.078
Withdrawal type				
Discontinuation	20 (34.5)	32 (68.1)	15 (71.4)	0.001
De-escalation	38 (65.5)	15 (31.9)	6 (28.6)	
OWS according to withdrawal type				
OWS after discontinuation	7 (35.0)	10 (31.3)	2 (13.3)	0.361
OWS after de-escalation	11 (28.9)	7 (46.7)	0 (0.0)	0.118
Total observation time, hours	18.8 ± 8.0	20.7 ± 6.0	22.3 ± 5.0	0.209
Duration of opioid infusion, days	5.5 [4.0–9.3]	5.0 [3.0–7.0]	6.0 [4.0–10.0]	0.456
Cumulative opioid dose, mg	5023.8 [2528.1–12110.1]	2090.4 [1043.3–4759.7] †	216.0 [48.0–588.0]†‡	< 0.0001
Symptoms of all patients/OWS (+)				
CAM	11 (19.0)/3 (16.7)	5 (13.2)/3 (25.0)	5 (23.8)/1 (50.0)	
Pupil	14 (24.1)/6 (33.3)	15 (31.9)/8 (47.1)	4 (19.0)/1 (50.0)	
GCS	0/0	2 (4.3)/1 (5.9)	0/0	
RASS	12 (20.7)/8 (44.4)	16 (34.0)/8 (47.1)	5 (23.8)/1 (50.0)	
Seizure	0/ 0	0/ 0	0/ 0	
Fever	7 (12.1)/4 (22.2)	7 (14.9)/3 (17.6)	0/ 0	
RR	44 (75.9)/17 (94.4)	32 (68.1)/13 (76.5)	13 (61.9)/2 (100.0)	
HR	25 (43.1)/13 (72.2)	17 (36.2)/10 (58.8)	10 (47.6)/1 (50.0)	

Table 2. Continue

Sputum	12 (20.7)/10 (55.6)	13 (27.7)/13 (76.5)	5 (23.8)/0
Secretion	12 (20.7)/10 (55.6)	15 (31.9)/13 (76.5)	3 (14.3)/0
Stool	16 (27.6)/10 (55.6)	11 (23.4)/5 (29.4)	3 (14.3)/1 (50.0)

Results are reported as n (%), mean ± SD, or median [interquartile range]. † vs. the remifentanil group. ‡ vs. the fentanyl group. OWS, opioid withdrawal syndrome; CAM, Confusion Assessment Method for the intensive care unit; GCS, Glasgow Coma Scale; RASS, Richmond Agitation-Sedation Scale; RR, respiratory rate; HR, heart rate.

The onset and duration of the 11 symptoms in all patients are shown in Figure 2. The onset of CNS symptoms did not differ among the three groups. The median onset time of changes in CAM and pupil size ranged from 7 to 12 hours. However, the onset time of change in RASS in the remifentanil group (4.5 ± 3.8 hours) was significantly earlier than that in the fentanyl group (5.8 ± 4.6 hours). There were many differences in onset time among the ANS symptoms between the three groups. The remifentanil group showed a faster onset time for both a change in respiratory rate (2.7 ± 1.9 hours) and pulse rate (4.1 ± 3.5 hours) than those in the fentanyl group. In addition, the morphine group showed a later onset time for increased oral secretion (14.3 ± 8.3 hours) than the other groups. Most of the ANS symptoms had similar durations of approximately 2–6 hours. The only difference was that the morphine group had a shorter duration of increased oral secretion than the other groups (1 hour). The duration of CNS symptoms was generally longer than that of the ANS symptoms, although there was no variation in the duration according to the type of opioid.

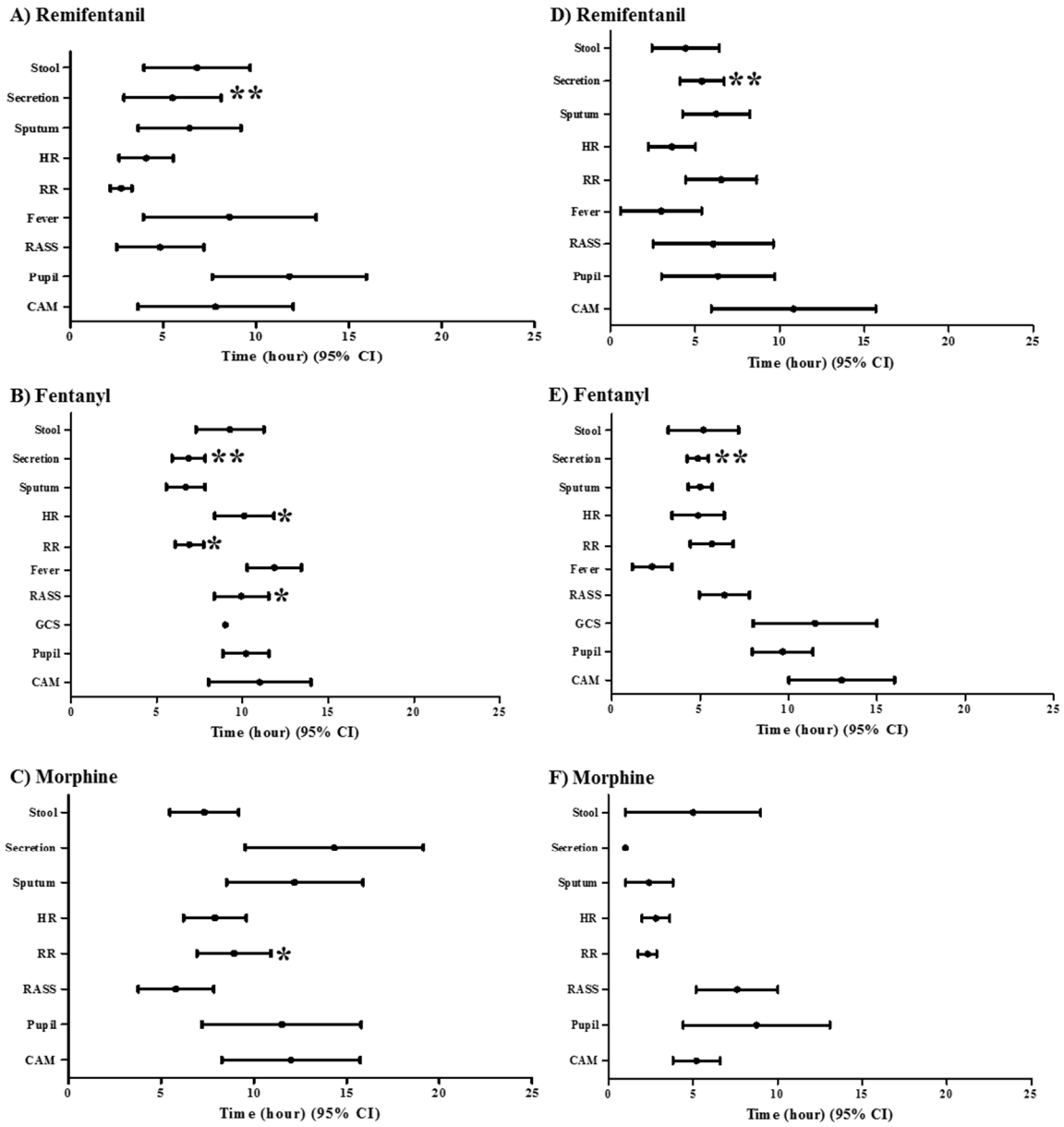

Fig. 2. Onset time and duration time of symptoms during 24 hours after discontinuation or de-escalation of opioid infusion. (A) Onset time of remifentanil group. (B) Onset time of fentanyl group. (C) Onset time of morphine group. (D) Duration time of remifentanil group. (E) Duration time of fentanyl group. (F) Duration time of morphine group.

*vs. the remifentanil group. **vs. the morphine group.

CAM, Confusion Assessment Method for the intensive care unit; GCS, Glasgow Coma Scale; RASS, Richmond Agitation-Sedation Scale; RR, respiratory rate; HR, heart rate.

To investigate risk factors, we conducted a multivariate analysis for covariables associated with OWS (Table 3). Although there were differences in history of opioid exposure, SOFA score, cumulative opioid dose, and use of sedatives among the three groups, univariate analysis showed a statistically significant association between OWS and septic shock, duration of opioid infusion, and total cumulative opioid dose. These variables, along with type of opioid and SOFA score, were included in the multivariable analysis. The stepwise Cox-proportional hazard model for multivariable analysis yielded two main predictors of OWS: the use of morphine as an analgesic (HR: 0.167, 95%: 0.037–0.743) and the duration of opioid infusion (HR: 0.566, 95%: 0.451–0.712). The final model was statistically significant (χ^2 [3] = 10.096, p = 0.018).

Table 3. Univariable and multivariable analyses of covariables associated with opioid withdrawal syndrome

	Univariable analysis			Multivariable analysis		
Variable	HR	95% CI	*p*	HR	95% CI	*p*
Comorbidity						
Respiratory failure	0.460	0.141–1.505	0.199			
Hematologic malignancy	1.602	0.770–3.333	0.207			
History of opioid exposure	0.544	0.211–1.405	0.209			
Alcoholism	1.749	0.725–4.218	0.213			
Septic shock	2.144	1.102–4.170	0.025			
Dialysis	1.659	0.796–3.459	0.177			
Type of opioid						
Remifentanil vs. fentanyl	1.509	0.763–2.985	0.237	1.514	0.736–0.357	0.404
Remifentanil vs. morphine	0.316	0.073–1.364	0.123	0.167	0.037–0.743	0.019
Sedative type						
No sedative	1.495	0.769–2.906	0.236			
SOFA score	1.091	1.989–1.202	0.081			
Duration of opioid infusion	0.587	0.471–0.733	< 0.0001	0.566	0.451–0.712	< 0.0001
Cumulative opioid dose ≥ 5500 mg	0.470	0.222–0.992	0.048			
Withdrawal type						
De-escalation	0.770	0.403–1.474	0.431			

SOFA, Sequential Organ Failure Assessment.

Discussion

For several decades, opioids have been used to support mechanically ventilated patients in the ICU [20]. In contrast with pediatric patients, few studies have been conducted to investigate the risks and side effects of opioids in adult ICU patients [12, 13, 21]. In the current study, a high frequency of OWS (29.4%) was observed in mechanically ventilated adult medical ICU patients, with the incidence being 31.0% in the remifentanil group, 36.2% in the fentanyl group, and 9.5% in the morphine group. A change of respiratory rate was the most common symptom of OWS, and increased oral secretion or sputum was the most specific symptom. In addition, the duration of opioid infusion and use of morphine showed a significant association with OWS.

The data presented here are similar to those reported in previous studies over the past two decades [12, 13]. One retrospective study evaluated 28 critically ill adult patients supported on mechanical ventilation for more than 7 days in the trauma and surgical ICU. Of these, nine patients were diagnosed with opioid or sedative withdrawal syndrome, although the study did not distinguish between the two syndromes [12]. Another recent

study showed the incidence of OWS to be 16.7% in patients receiving mechanical ventilation for > 72 hours [13]. However, this study did not report the incidence according to opioid type and evaluated OWS using the DSM-5 criteria only. Despite the differences between the three studies in terms of study design, reason for admission and assessment tool used, it is evident that OWS is highly prevalent in adult ICU patients.

Few studies have reported the symptoms of OWS in critically ill adult patients. The only previous study is a small series of nine patients with opioid or benzodiazepine withdrawal syndrome [12]. The common symptoms were irritability (100%), hypertension (88.9%), tachycardia (77.8%) and tachypnea (44.4%). A case series of three patients with remifentanil withdrawal syndrome showed that anxiety, hypertension, and tachycardia occurred in all three patients; tachypnea, dilated pupils, and sweating were observed in two of the three patients [22]. Although there are some differences in the frequency of symptom reporting between previous studies and the current study, the occurrence of symptoms such as tachycardia, tachypnea, and anxiety was similar. However, a key difference is the occurrence of increased oral secretion and sputum in the current study,

which showed a high specificity for OWS. Additional, prospective studies will be required to accurately evaluate the symptoms associated with OWS further.

The current study showed a significantly lower incidence of OWS in patients who received morphine than in those receiving remifentanil or fentanyl, which is consistent with previous studies of pediatric patients [4, 8, 23, 24]. Animal studies have shown differences between the mechanisms involved in the antinociceptive effects of compounds such as fentanyl and its analogs and morphine. Morphine interacts differently with the *mu* receptor than fentanyl analogs, which may explain its lack of *mu* receptor desensitization [25-27]. These data may explain the difference in the incidence of OWS seen in patients receiving morphine versus those receiving remifentanil or fentanyl. Finally, this study suggests that careful consideration should be given when selecting an opioid for the treatment of critically ill adult patients requiring mechanical ventilation.

In general, the frequency of OWS is thought to increase as the duration of opioid administration increases [28]]. However, the current study showed the opposite result, i.e., that a longer duration of opioid infusion decreased the incidence of OWS. A few previous

studies have evaluated the association between duration of opioid use and withdrawal syndrome [4, 7, 29]. In two pediatric studies, adjusted models showed that a longer duration of opioid treatment was a risk factor for the development of OWS. However, a study of adult patients did not show an association between the duration of opioid use and withdrawal syndrome [13]. As all patients were supported by mechanical ventilation for at least 3 days in the current study, it is possible that this may have affected the results and further large scale trials are required to confirm these observations.

This study has some limitations, in addition to the small sample size. First, differences in demographic characteristics were seen between the treatment groups. Patients in the remifentanil group had a lower proportion of opioid exposure than those in the other groups, and patients in the fentanyl group had higher SOFA scores than those in the morphine group. Therefore, randomized, controlled trials are required to exclude factors that may influence the rate of OWS. Secondly, OWS was diagnosed using assessment tools that have not yet been validated, as a validated assessment tool has not yet been developed for use in critically ill adult patients. Finally, the evaluation period was limited

to 24 hours. It is known that OWS may occur some days after cessation of opioid therapy, based on the criteria of DSM-5, and the context-sensitive concentration of fentanyl is more than 5 hours [30]. Therefore, it is possible that patients who exhibited withdrawal symptoms after the evaluation period may have been missed.

Conclusion

This study suggests that OWS is frequently observed in mechanically ventilated adult patients who received continuous infusion of opioids for more than 3 days. The most common symptoms were a change in respiratory or pulse rate in all patients. The use of morphine may be associated with a decreased risk of OWS. Further prospective studies are required to confirm these preliminary results.

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국문요약

연구 배경: 마약성 진통제를 사용하다 이를 중단하거나 용량이 감소되면 마약성 진통제 중단 증후군이 발생할 수 있다. 소아 중환자에서는 마약성 진통제 중단 증후군이 흔하며, 중요한 부분 중 하나이다. 그러나 성인 중환자에서는 마약성 진통제 중단 증후군에 대한 자세한 연구가 시행되지 않았다. 본 연구에서는 성인 중환자에서 마약성 진통제 중단 증후군의 발생률, 특징 그리고 위험인자에 대하여 보고자 하였다.

연구 방법: 2016 년 11 월부터 2017 년 10 월까지 국내의 3 차 의료기관인 서울아산병원의 내과계 중환자실에 입원하여 3 일 이상 기계환기 치료를 받았고 한 종류의 마약성 진통제만을 지속 주입받은 환자를 대상으로 후향적 연구를 진행하였다. 마약성 진통제 증후군은 마약성 진통제의 지속 주입의 중단 혹은 최고 용량의 절반 미만으로 감소한 이후부터 최대 24 시간까지 평가하였다. 중추 신경계 혹은 자율 신경계 증상이 3 개 이상 있는 경우를 마약성 진통제 중단 증후군으로 정의하였다.

연구 결과: Remifentanil 58 명, fentanyl 47 명 그리고 morphine 21 명으로 총

126 명의 환자에서 각각 31.0%, 36.2%, 9.5%로 마약성 중단 증후군이 발생하였다 (p = 0.078). 가장 흔한 증상은 호흡수의 변화였다 (remifentanil 94.4%, fentanyl 76.5%, morphine 100%). 다변량 Cox 비례 위험 모델에서는 morphine 의 사용 (위험비 0.17, 95% 신뢰구간 0.037-0.743) 및 마약성 진통제 주입 기간 (위험비 0.566, 95% 신뢰구간 0.451-0.712)이 마약성 진통제 중단 증후군과 관련 있는 것으로 나타났다.

연구 결론: 마약성 진통제를 지속 주입하는 성인 중환자에서 마약성 진통제 중단 증후군은 흔하게 발생한다. 마약성 진통제 종류에 따른 중단 증후군 발생률의 통계학적으로 유의미한 차이는 없었다. 그러나 마약성 진통제 주입 기간이 짧은 환자 그리고 morphin 을 지속 투입 받은 환자에서 중단 증후군이 덜 발생하는 경향을 보였다.

중심 단어: 진통제, 약물 금단 증후군, 발생률, 집중 치료실