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■ Original Article ■

Comparison of Morphine and Remifentanil on the Duration of Weaning from Mechanical Ventilation

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Background: A randomized, multicenter, open-label, parallel group study was performed to compare the effects of remifentanil and morphine as analgesic drugs on the duration of weaning time from mechanical ventilation (MV).
Methods: A total of 96 patients with MV in 6 medical and surgical intensive care units were randomly assigned to either, remifentanil (0.1-0.2 mcg/kg/min, n = 49) or morphine (0.8-35 mg/hr, n = 47) from the weaning start. The weaning time was defined as the total ventilation time minus the sum of controlled mode duration.
Results: Compared with the morphine group, the remifentanil-based analgesic group showed a tendency of shorter weaning time (mean 143.9 hr, 89.7 hr, respectively: p = 0.069). Secondary outcomes such as total ventilation time, successful weaning rate at the 7th of MV day was similar in both groups. There was also no difference in the mortality rate at the 7th and 28th hospital day. Kaplan-Meyer curve for weaning was not different between the two groups.
Conclusions: Remifentanil usage during the weaning phase tended to decrease weaning time compared with morphine usage.

Key Words: mechanical ventilation; morphine; remifentanil; ventilator weaning.

Introduction

Most patients with mechanical ventilation (MV) in the intensive care unit (ICU) receive analgesic and/or sedative agents to control pain, relieve agitation and anxiety, and reach a compliance with MV.[1,2] A safe and effective strategy that ensures the patients' comfort while maintaining a light level of sedation is usually associated with improved clinical outcomes.[3] Opioids, such as fentanyl, hydromorphone, morphine, and remifentanil, are the primary agents for managing pain in ICU patients.[4]

All opioids have sedative properties to various degrees at high doses.[1] The pharmacodynamic effects of conventional opioids such as fentanyl and morphine can be often prolonged when administered through several days, as a result of re-distribution and accumulation.[5] Especially morphine is regarded as the gold standard of analgesics. It has a late peak time (up to 80% effect at 15 minutes, but peak analgesic effect at 90 minutes) and duration (3-4 hours) when it is applied intravascularly.[6,7] This prolonged effect of morphine can induce a suppression of respiratory drive and potentially delay the weaning from MV.[2]

Remifentanil hydrochloride is a potent, selective μ-opioid receptor agonist with a rapid onset time (about 1 minute), and a quick steady-state achievement.[5] Its rapid metabolism by non-

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specific esterases in the blood and tissue (2 to 3 minutes of half-life) is independent of dose and application time, as well as of the patients' renal and hepatic functions.[5,8,9] Because of this benefit, it is easy to titrate and can be given in relatively high doses for prolonged periods of time without the risk of accumulation.[9,10] Therefore, remifentanil can be regarded as the ideal agent for critically ill patients.

We performed the present study to compare the efficacy and duration of MV and its weaning therefrom, between a remifentanil-based analgesia group and a morphine-based analgesia group in medical and surgical ICUs. We hypothesized that compared with morphine, the use of remifentanil leads to a shortened weaning time from MV.

Materials and Methods

This randomized, multicenter, open-label, parallel group study was conducted from January 1, 2011 to December 31, 2012, in the surgical and medical ICU of 6 hospitals in South Korea. The institutional review boards of all hospitals approved the study protocol, and informed consents were obtained from the legal representatives of all patients.

The patients' criteria for being eligible for this study were age older than 18 years, MV requirement more than 48 hours, and recovery phase from the acute phase of acute respiratory failure. We excluded patients who were expected to need a permanent ventilator treatment and those under continuous renal replacement therapy. All eligible patients (n = 96) were randomly assigned to either morphine (n = 47) or remifentanil (n = 49) treatment.

Definition of terms:

1) Total ventilation time: the time period from the start of MV to the successful weaning end point.

2) Weaning time: (total ventilation time) − (time of ventilation with the controlled mode), however, if the patient was weaned with pressure control, the duration of the controlled mode was as follows;

a. If the peak pressure control level was more than 20 cm H_2O: time of ventilation spent 16 cmH_2O or above

b. the peak pressure control level was less than 20 cmH_2O : time of ventilation spent at 70% or above of peak pressure control level

3) Weaning trial: start of weaning according to the following criteria;

a. Oxygenation: PaO_2 > 60 mmHg with FiO_2 < 0.4, PaO2/FiO_2 > 150, SaO_2 > 90%, PEEP < 5 cmH_2O, and minute volume < 15 L/min.

b. Vital signs: mean arterial pressure > 60 mmHg without vasopressor, heart rate < 140/min, 35°C < body temperature < 38°C, and respiratory rate < 35/min.

c. Clinical status: resolution of acute disease phase, no newly developed definite pulmonary infiltration, Ramsay sedation score 2-4, hemoglobin > 7 g/dl, pH > 7.30, electrolyte within normal range, no active bleeding, no increased intracranial pressure, no bronchospasm, no untreated coronary arterial disease, and no specific treatment such as nitric oxide gas, prone position or operation plan etc.

4) Successful weaning: more than 48 hours of spontaneous breathing with a T-piece or in the extubated status. Successful weaning marked the cessation of MV.

5) Primary weaning failure: restart of MV within 48 hours from the weaning end.

6) Secondary weaning failure: restart of MV between 48 hours and 7 days from the weaning end.

7) Unsuccessful weaning: no successful weaning within 7 days from the study enrollment.

Two analgesic drugs, morphine and remifentanil, were used following the protocol from the first weaning trial for 7 days (Fig. 1). If the patient failed to be weaned, the clinician could select analgesic or sedative drugs freely after 7 days from the weaning start. The amount of other drugs such as midazolam, lorazepam, haloperidol, or seroquel was recorded daily. In case

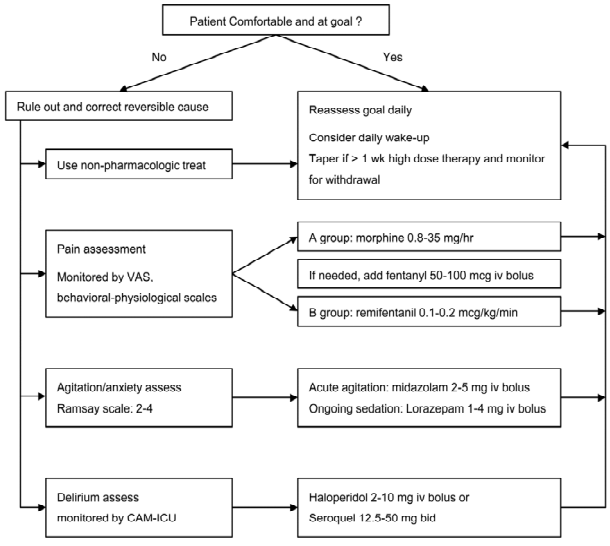

Fig. 1. Algorithm showing the analgesic or sedative drug use during the weaning period.

of dys-synchrony with the ventilator or agitation even after the bolus injection of sedative agents, application of antipsychotics like haloperidol or seroquel was considered. To decrease the discrepancies between the different hospitals, we made a ventilator setting guideline for the weaning period (Fig. 2).

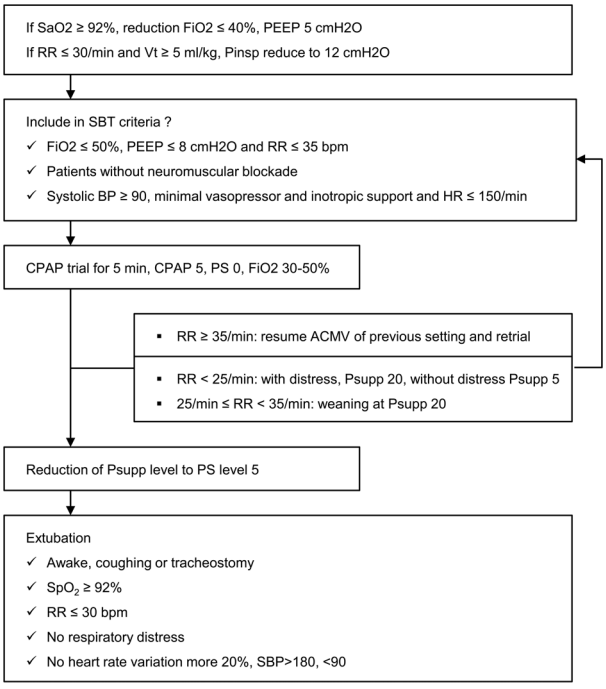

Fig. 2. Ventilator setting guideline during weaning period.

The primary end-point of this study was weaning time and the secondary end-point were total ventilation time, successful weaning rate, ICU length of stay, and primary and secondary weaning failure rates. Statistical analysis was performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). A p value of less than 0.05 was considered statistically significant.

Results

A total 96 patients were recruited in this study (47 with morphine and 49 with remifentanil). The characteristics and baseline clinical assessments of the 96 patients are summarized in Table 1. There was no significant difference between morphine group and remifentanil group with regards to gender, age, height, weight (actual and predicted body weight), underlying diseases, reason of MV, and ICU severity scoring values (acute physiology and chronic health evaluation II and sequential organ failure assessment). Among the underlying diseases, the ratio of chronic obstructive pulmonary disease or asthma of two groups also did not show any differences.

Table 1. Patient characteristics and baseline clinical assessments

Characteristics	Morphine (n = 47)	Remifentanil (n = 49)	p value
Gender			0.295
Male (n = 59, 61%)	26 (55)	33 (67)	
Female (n = 37, 39%)	21 (45)	16 (33)	
Age, yr	66.0 ± 15.2 (70)	66.0 ± 14.5 (68)	0.704
Height, cm	160.7 ± 8.9 (159)	162.1 ± 9.4 (160)	0.517
Actual body weight, kg	58.1 ± 10.2 (60.0)	60.6 ± 13.4 (59.7)	0.190
Predicted body weight, kg	56.4 ± 9.8 (56.6)	58.24 ± 10.1 (61.5)	0.707
Underlying diseases	41 (84)	51 (91)	0.374
Hypertension	19 (40)	19 (39)	1.000
Diabetes Mellitus	16 (34)	16 (33)	1.000
Ischemic heart disease	3 (6)	4 (8)	1.000
Nephropathy	1 (2)	1 (2)	1.000
Postoperative state	4 (9)	6 (12)	0.741
Cancer	11 (23)	13 (27)	0.815
Others	26 (55)	29 (59)	0.837
Reasons of MV			0.525
Acute respiratory failure	44 (94)	42 (86)	
Acute exacerbation of chronic respiratory failure	2 (4)	3 (6)	
Acute and chronic respiratory failure combination	1 (2)	1 (2)	
Postoperative conditions	0 (0)	2 (4)	
APACHE II score on the first ICU day	21.4 ± 7.8 (20)	23.4 ± 8.7 (25)	0.456
APACHE II score on the first ventilator day	19.4 ± 8.6 (19)	22.1 ± 9.6 (24)	0.244
SOFA score on the first ICU day	7.4 ± 3.4 (7)	8.5 ± 4.2 (9)	0.186
SOFA score on the first ventilator day	6.9 ± 3.8 (7)	8.1 ± 4.4 (9)	0.311

Variables are presented as mean ± standard deviation (median) or n(%). MV: mechanical ventilation; APACHE: acute physiology and chronic health evaluation; ICU: intensive care unit; SOFA: sequential organ failure assessment.

Table 2. Medication until enrollment

Drug	No. of patients Duration of drug use (days) Total amount (mg)		p value
	Morphine	Remifentanil	
Morphine	37	37	
	2.0 ± 2.6 (1)	2.1 ± 2.9 (1)	0.810
	90.4 ± 152.3 (10.0)	110.6 ± 192.7 (20.0)	0.424
Remifentanil	24	28	
	5.0 ± 3.0 (4)	5.0 ± 3.9 (4)	0.158
	60.1 ± 96.2 (26.6)	39.3 ± 40.1 (26.6)	0.108
Fentanyl	28	29	
	3.6 ± 2.6 (3)	3.2 ± 2.3 (2)	0.816
	16.7 ± 24.2 (7.3)	11.4 ± 15.9 (1.0)	0.334
Midazolam	37	29	
	4.4 ± 2.8 (4)	4.7 ± 4.7 (3)	0.102
	198.9 ± 221.2 (106.7)	275.5 ± 427.4 (105.5)	0.025
Lorazepam	7	10	
	2.1 ± 1.2 (2)	1.7 ± 0.7 (2)	0.038
	5.1 ± 4.4 (3.0)	4.3 ± 2.2 (4.0)	0.031
Atracurium	15	14	
	3.6 ± 2.2 (3)	2.1 ± 1.5 (2)	0.099
	846.0 ± 1014.5000 (530.8)	424.5 ± 617.1 (75.0)	0.133
Ketamine	12	10	
	3.0 ± 2.0 (2)	3.6 ± 2.7 (2)	0.880
	1503.2 ± 2020.0 (655.1)	2364.6 ± 3162.4 (716.2)	0.401
Seroquel	9	9	
	4.0 ± 3.5 (4)	3.8 ± 2.5 (4)	0.223
	141.7 ± 163.5 (62.5)	172.2 ± 246.4 (75.0)	0.592

All data are presented as mean ± standard deviation (median).

Table 3. Exposure to a study medication from the weaning start point

Drug	No. of patients Duration of drug use (days) Total amount (mg)		p value
	Morphine	Remifentanil	
Morphine	47	0	
	4.4 ± 2.2 (1)	0	
	226.5 ± 279.2 (10.0)	0	
Remifentanil	0	49	
	0	4.1 ± 2.4 (4)	
	0	29.9 ± 34.3 (12.0)	
Fentanyl	12	15	
	1.4 ± 0.7 (1)	1.8 ± 1.6 (1)	0.274
	4.2 ± 9.1 (0.2)	2.5 ± 7.7 (0.2)	0.551
Midazolam	31	34	
	1.7 ± 0.5 (1)	1.7 ± 0.4 (0)	0.188
	1.4 ± 2.0 (??)	0.9 ± 1.6 (??)	0.090
Lorazepam	46	6	
	1.9 ± 0.3 (1)	1.9 ± 0.3 (1)	0.817
	2.3 ± 2.4 (6.0)	1.3 ± 0.8 (2.0)	0.080
Seroquel	11	10	
	4.6 ± 2.7 (4)	4.4 ± 2.5 (4)	0.782
	331.8 ± 409.8 (100.0)	170.0 ± 159.0 (150.0)	0.013

All data are presented as mean ± standard deviation (median).

Until study enrollment, physicians could select sedative and analgesic agents freely according to their clinical decision. No statistical difference between the two groups existed for the drugs morphine, remifentanil, fentanyl, ketamine, and seroquel regarding the mean duration of application and the total amount (Table 2). The patients of remifentanil group received more

Table 4. Clinical correlations between the study medications and weaning outcomes

Characteristics	Morphine (n = 47)	Remifentanil (n = 49)	p value
Total ventilation time, hr	535 ± 1493	283 ± 206	0.107
Success rate of weaning at the 7th MV day	60.9	55.1	0.678
Primary weaning failure	57.1	61.2	0.831
Secondary weaning failure	43.9	38.3	0.666
Weaning time, hr	144 ± 176	90 ± 89	0.069
Total hospital admission period, d	45.6 ± 39.9	45.9 ± 41.9	0.760
ICU length of stay, d	17.2 ± 10.6	17.6 ± 13.8	0.670
Mortality at the 7th ICU day	6.8	4.2	0.667
Mortality at the 28th hospital day	20.5	16.7	0.789

Data are presented as mean ± standard deviation or %. Primary weaning failure, restart of MV for more than 24 hours within 48 hours after the start of weaning; Secondary weaning failure, restart of MV for more than 24 hours between 48 hours and 7 days after the start of weaning. MV: mechanical ventilation; ICU: intensive care unit.

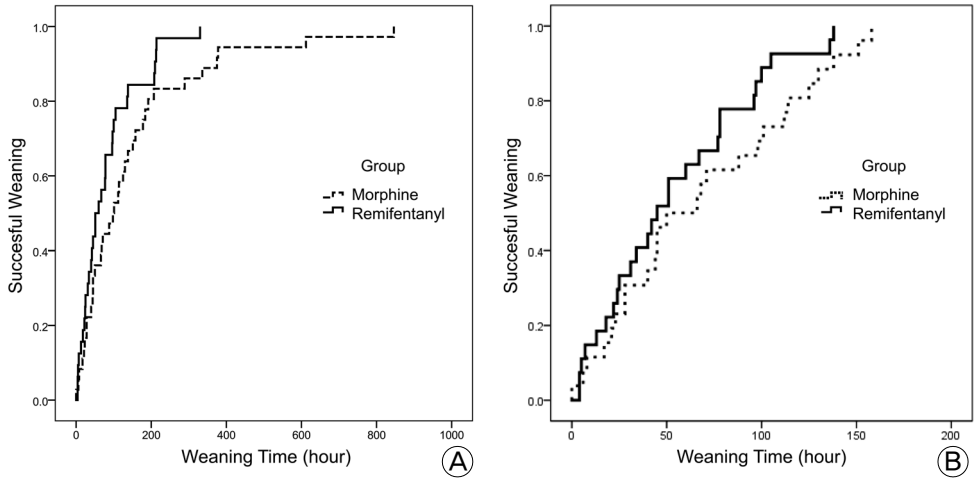

Fig. 3. Kaplan Meier curves for the weaning of all patients (A) and for only those who had a weaning time of less than 7 days (B).

amount of midazolam compared to fentanyl group (275.5 mg vs. 198.9 mg, p = 0.025) while lorazepam amount was less in remifentanil group (4.3 mg vs. 5.1 mg, p = 0.031). Atracurium, a muscle relaxant, was used longer in morphine group, however, it was not statistically significant (3.6 days vs. 2.1 days, p = 0.099).

From the start of weaning, the patients of the morphine group received an average total amount of 226.5 mg of morphine as the main analgesic drug over an average period of 4.4 days. The patients of the remifentanil group also received mainly remifentanil as an analgesic drug; mean duration of remifentanil use, 4.1 days and total amount, 29.9 mg, respectively. The use of fentanyl, midazolam, and lorazepam was not different between in both groups (Table 3). However, although the application duration of seroquel was almost the same in both groups, the patients in the morphine group received a larger amount than those in the remifentanil group (331.8 mg vs. 170.0 mg, p = 0.013).

The rate of successful weaning at the 7th day of MV was almost identical in both groups (Table 4). The rate of primary and secondary weaning failures also did not show the statistical differences. The weaning time was longer in morphine group compared to remifentanil group (143.9 hours vs. 89.7 hours, p = 0.069, Fig. 3). There was no difference in view of ICU length of stay, hospital admission period, and mortality rate at the 7th day in ICU day or the 28th day in the hospital.

The number of people who could be weaned in less than 7 days was 26 in the morphine group and 27 in the remifentanil group. Comparing only these patients, the weaning time in the morphine group was still longer than in the remifentanil group (68.3 hours vs. 53.6 hours, p = 0.181). Hospital admission period, ICU length of stay, and ventilation duration did not show any difference.

Discussion

Remifentanil is rapidly hydrolyzed by non-specific plasma cholinesterases to nearly inactive metabolites, which results in short-term impact and prevents accumulation.[11] In the present study, we compared the clinical implications of remifentanil- and morphine-based analgesia during the weaning period from

MV. The clinical outcomes of our study are somewhat difficult to interpret as they do not unambiguously point to one of two drugs as the superior one. However, the tendency of remifentanil to reduce the total ventilation and the weaning time, compared to morphine can clearly be seen. This outcome is in line with previously published data, as Breen et al.[1] reported a significantly reduced duration of MV (Δ = 53.5 hours, $p = 0.033$) and of the weaning time (Δ = 26.6 hours, $p < 0.001$) when using remifentanil instead of morphine as a sedative agent.

"Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the ICU" mentioned that when titrated to similar pain intensity and end-points, all opioids administered IV exhibit similar analgesic efficacy and are associated with similar clinical outcomes (for example, duration of MV or length of stay in ICU).[3] In contrast, this study shows the tendency of remifentanil to decrease the duration of MV and weaning time compared to morphine, which may be due to stable analgesia of remifentanil because of its rapid onset and offset of action, and its therefore more controlled and stable analgesic behavior.[12]

Delayed weaning from the start of weaning trial can have many reasons such as severity of underlying diseases, patient's condition change or duration of MV before weaning trial etc. To exclude the possible bias by delayed weaning, we also analyzed only these who could be weaned in less than 7 days. Remifentanil group of less than 7 days' weaning time also could not reveal the statistical superiority in weaning time decrease compared to morphine group. However, the Kaplan-Meier curve of a weaning time showed more discrepancy in patients with less than 7 days weaning time compared to whole study enrolled patients (Fig. 3).

In remifentanil group, patients showed less need of sedative agents such as midazolam and lorazepam during the weaning time (Table 3). This can be a reflection of hypnotic drug sparing effect of remifentanil.[13,14] Remifentanil group also showed less use of anti-delirium drug, seroquel, during weaning period ($p = 0.013$). Haloperidol was used only in one case in each group. Benzodiazepine use can be a risk factor for the development of delirium[3] and less use of benzodiazepine during weaning period can be a reason of less delirium incidence and less use of seroquel in remifentanil group. However, until study enrollment, midazolam was used much more in remifentanil group while as lorazepam was used more in morphine group and until enrollment, used day and amount of seroauel was not different between two groups (Table 2). Therefore, we cannot mention that less delirium in remifentanil group is due to less use of benzodiazepine only.

Several studies have reported the deleterious effects of remifentanil such as severe bradycardia, hypotension and asystolic episodes.[15-17] In this study, severe bradycardia or hypotension was not encountered in at all. Slow injection of a bolus dose and strict titration of the infusion rate seemed to reduce the incidence of these side effects.[18,19]

This study has certain limitations. The first limitation of this study is a small number of enrolled patients and this might be the main reason of non-statistical different result of this study. We planned total 240 cases enrollment with 120 patients in each group in 6 hospitals. However, the enrollment was not easy in each hospital because of the strict study protocol and we also decided to exclude continuous renal replacement therapy cases for getting rid of a bias factor of this comparison study. Second, it is an open-label study and it was difficult to make a double-blinded design for our study. Third, because of diversity of used drug until study enrollment, we could not distinguish the effect of remifentanil only during weaning period clearly. If we designed to use remifentanil from the first intent during the whole MV period, we might get more definite effect of remifentanil. Forth, one of the reasons why we could not get a statistical difference between morphine and remifentanil can be patients' diversity including medical and surgical patients. Many previous studies were usually performed with relatively unique study group character such as post surgical patients.[1,14,20] Further study about remifentanil's weaning efficacy in only medical patients is expected.

In conclusion, remifentanil-based analgesia during the weaning phase from MV in critically ill patients tended to reduce the duration needed for weaning from MV compared to morphine-based analgesia. The use of remifentanil during weaning phase resulted in lower benzodiazepine and seroquel requirement.

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