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Effectiveness of Remifentanil for Analgesia Based Sedation in Mechanically Ventilated Patients

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ABSTRACT
Background: *The administration of analgesics and sedatives are vital for mechanically ventilated patients for providing comfort and reducing stress, as well as to prevent delay in recovery and ventilator weaning. Hypnotic based regime using midazolam-fentanyl combination is commonly used for sedation and analgesia in intensive care unit. The hypnotic component is titrated to a desired level of consciousness and analgesia given as per thought of physicians.* ***Objectives:*** *This study was conducted to explore effectiveness of remifentanil for optimum sedation and analgesia in comparison to midazolam-fentanyl combination in mechanically ventilated patients.****Methods:*** *The randomized controlled trial was carried out in the ICU at the Department of Anaesthesia, Pain, Palliative & Intensive Care Medicine, Dhaka Medical College from March, 2020 to March, 2021. Total 64 mechanically ventilated patients were included in the study according to the selection criteria. But 60 patients could only be able to be evaluated excluding 4 male patients.Ethical issues were ensured and written informed consent was taken before data collection from the legal guardian. All collected data were registered, documented and analyzed in the statistical program Statistical Package for Social Science (SPSS) version 24.****Results:*** *Total number of patients was 60, mean age of group A and group B was 40.8 ± 11.8 and 41.1± 11.2 years respectively. Out of 30 patients 19 were male and 11 were female in group A and out of 30 patients 18 were male and 12 were female in group B. There was no significant difference in relation to age, gender and other demographic characteristics. Remifentanil provided optimum sedation in comparison to midazolam and fentanyl combination group. In remifentanil group mean RASS score was between -1 to -2. And in midazolam-fentanyl combination group it was between -1 to -3. In group A mean COPT score was below 3 and in group B it was below 4. The requirement, frequency and dose of recue drug (morphine) was more in B. Duration of infusion of study medication was longer in group B. There was acceptable hemodynamic stability in both groups along with expected frequencies of hypotension and bradycardia.****Conclusion:*** *Remifentanil was effective for optimum sedation and analgesia in comparison to combination of midazolam and fentanyl in mechanically ventilated patients.*
Keywords:*Analgesic, Sedative, Ventilated patients, Midazolam-fentanyl.*

I. INTRODUCTION

Analgesia based sedation provides comfort to mechanically ventilated patients in the intensive care unit. Mechanical ventilation creates physiological and psychological stress on these patients. Patients cannot talk, eat or swallow for the endotracheal tubes. They are also confused, alone and undergo patient-ventilator asynchrony with being uncomfortable during endotracheal suctioning. So, they are always under psychosomatic stress. Patients also experience fear of the unknown and death, sleep deprivation, agitation and pain. They are also dissatisfied for being restrained, immobile and always in continuous noise. To promote tolerance to the ICU environment effective sedation and analgesia both are needed for providing patient safety with comfort being on the life-supporting therapy (mechanical ventilation). So, the goal of providing adequate comfort and analgesia to the patients on mechanical ventilation can be achieved by analgesia-based sedation technique. It provides patient comfort by controlling pain, breathing difficulty and anxiety with facilitating patient- ventilator interactions. It

reduces oxygen consumption and provides amnesia. It prevents convulsions and maintains function of brain. It also aids in applying neuromuscular blockage and compliance with mechanical ventilation.

There is no recognized ideal sedative technique being used universally in mechanically ventilated patients worldwide. In a survey of 164 ICUs in the United States, 18 different sedative agents were used. The most common agents were morphine sulfate, lorazepam, midazolam, diazepam and haloperidol. Intensive care units of the United Kingdom used 11 different agents in another survey. These surveys showed a major variation in sedative techniques for mechanically ventilated patients. Short term sedation from 10 minutes to 24 hours in cardiac surgery patients and surgical or mixed ICU patients was achieved by propofol, midazolam, diazepam, morphine, pethidine, alfentanil. These drugs Were studied as a single agent for sedation. [1] The first sedative study was comparing propofol and midazolam in cardiac surgery patients by.[2] In the study percentage of time of target sedation levels was not satisfactory for both sedative agents and length of ICU stay was not reduced: but time to extubation was decreased. Long term sedation for more than 24 hours was evaluated in many trials. They compared propofol with midazolam; midazolam with lorazepam; ketamine with fentanyl. Combined agents were also studied comparing fentanyl with midazolam versus ketamine with midazolam. These trials were done from 1992. But no study was able to show any satisfactory level of target sedation with analgesia. Sedation should be only used after properly addressing analgesic need which can only be achieved by analgesia-based sedation regime. It provides comfort and reduction in anxiety while being on mechanical ventilation.[1] So, in this light of lack of effectivesedative technique in mechanically ventilated patients it is a major concern to develop a good strategy to provide sedation while giving adequate comfort with analgesia. This can be provided by ensuring analgesia-based sedation technique using analgesic drug such as remifentanil.

The most frequently used sedatives in the ICU are benzodiazepines like midazolam, lorazepam, propofol and dexmedetomidine. [3] Midazolam is commonly used for sedation in a conventional hypnotic based sedation technique. But it is metabolized by CYP3A enzyme and so there is clinically considerable interaction with inducers and inhibitors of CYP3A4. Erythromycin, fluconazole, itraconazole and voriconazole have been shown to reduce the clearance of intravenous midazolam inhealthy volunteers by 50%o70%. [4] Propofol has a cardiovascular depressant effect. It may lead to dose-dependent hypotension and bradycardia. There is also risk of pain on injection, propofol infusion syndrome, hypertriglyceridaemia and accidental microbial contamination with propofol infusion. [5]Dexmedetomedine has cardiovascular risks as it decreases heart rate and cardiac output for its depressed sympathetic activity in a dose-dependent manner. [6]

Analgesia-based sedation with remifentanil is a useful option for mechanically ventilated patients. [7] Remifentanil is a derivative of fentanyl with an ester linkage to propanoic acid. It is ultra-short acting and at the - receptor it displays analgesic effects. [8] It has been used in induction and maintenance of general anesthesia and as an analgesic in mechanically ventilated critically ill patients. It has a rapid onset of action (1 minute) and a rapid offset of action following discontinuation (3-10 minutes). Remifentanil is rapidly metabolised via extrahepatic, nonspecific blood and tissue esterases. This organ-independent elimination property makes it helpful for the critically ill ICU patients with various degree of organ dysfunction. [9]So, in critically ill patients these traits make it an ideal agent. It is easy to titrate and can be given without risk of accumulation or delayed offset of effects. It allows the opioid to be used as the chief drug to provide patient comfort with sedation. [10] In ICU patients, remifentanil generally showed satisfactory degree of hemodynamic stability including during the procedures such as endotracheal suctioning. [11] Among mechanically ventilated ICU patients, recovery of spontaneous respiration was better with remifentanil than with morphine following extubation. [12]

II. METHODOLOGY

This randomized controlled trial was carried out in the ICU at the Department of Anaesthesia, Pain, Palliative & Intensive Care Medicine, Dhaka Medical College from March, 2020 to March, 2021. Total 157 patients admitted in ICU of Dhaka Medical College Hospital were screened for the study. Informed written consent was obtained from 64 patients who fulfilled inclusion and Nelusion criteria. But four patients were excluded from the study after recruitment. Among the excluded patients, attendant of 1 patient discontinued treatment in group A; and 1 patient attendant in group A and 2 patients' attendants in group B did not give consent for continuation of the study. The patients developed hemodynamic instability during study period were also excluded from the study. 2 patients in group A and 4 patients in group B developed hypotension; and 1 patient in group A and 3 patients in group B developed bradycardia. For statistical purpose number of sample was increased. So, 60 patients were able to be evaluated. There were 30 patients in group A and 30 patients in group B. After taking consent and matching eligibility criteria, data were collected from patients on variables of interest using the predesigned structured questionnaire by interview, observation. Statistical analyses of the

results were be obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24).

III. RESULTS

Table I: Demographic characteristics of the patients (n=60)

Characteristics	Group A (n=30)	Group B (n=30)	P-value
Age in years			
Mean ± SD	40.8 ± 11.8	41.1 ± 11.2	0.929^{ns}
Sex			
Male	19 (63.3%)	18 (60%)	0.5^{ns}
Female	11 (36.7%)	12 (40%)	
Mean height (cm)	162.69 ± 6.9	161.71± 5.9	0.56^{ns}
Mean weight (kg)	58.33 ± 7.40	57.43 ± 6.5	0.62^{ns}

Demographic characteristics of the patients are shown in Table I. Unpaired student t-test was performed to compare age, height and weight between two groups; and chi-squared Test was performed to compare gender between two groups.

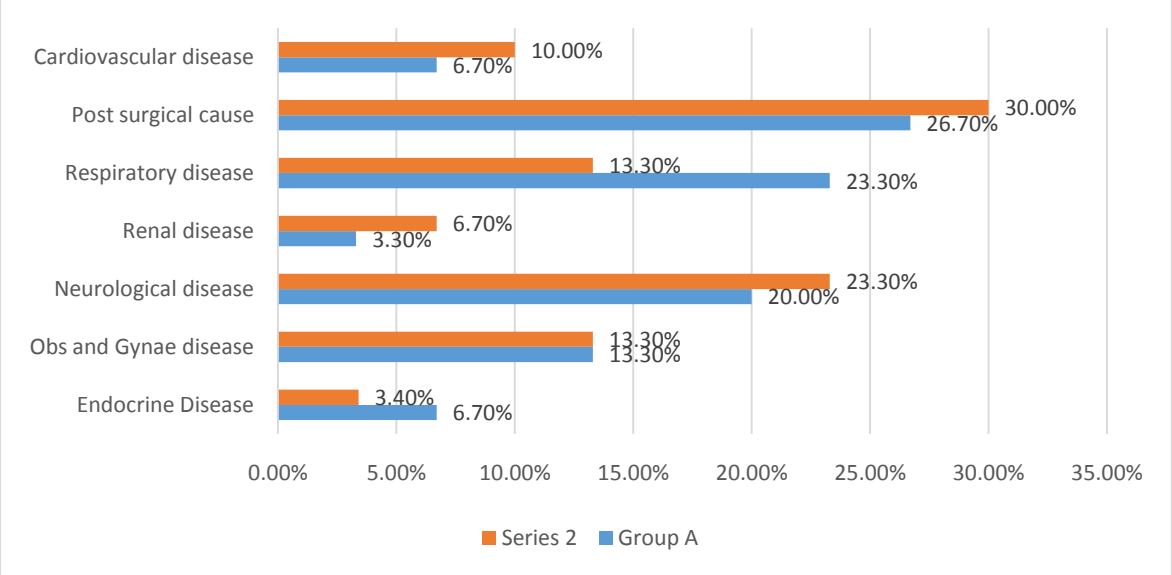

Figure I: Clinical diagnosis of study patients (n=60)

Figure Ishow clinical diagnosis of the patients of both groups. Among 60 patients of group A 6.7% had endocrine disease,13.3% had obstetric and gynecological disorder, 20% had neurological disease, 3.3%had renal disease, 23.3% had respiratory disease, 26.7% with post-surgical causes and6.7% had cardiovascular diseases. Whereas in group B out of 60 patients 3.3%% hadendocrine disease, 13.3% had obstetric and gynecological disorder, 23.3% hadneurological disease, 6.7% had renal disease, 13.3% had respiratory disease, 30% with post-surgical causes and 10% had cardiovascular diseases.

Table II: Comparison of both groups according to RASS score (n= 60)

Variables		Group A (n=30)	Group B (n=30)	P-value
RASS	Day 1	-1.77± 1.65	-2.53 ± 1.92	0.103^{ns}
	Day 2	-1.87 ± 1.81	-2.10 ± 2.38	0.671 ^{ns}
Score				
	Day 3	-1.33 ±1.9	-1.5 ± 1.4	0.701^{ns}

Table II shows comparison of RASS score of both groups in day 1, day 2 and day 3. In group A RASS score was between -1 to -2. And in group B it was between -1 to -3.

Table. III: Comparison of both groups according to CPOT score (n= 60)

Variables		Group A (n=30)	Group B (n=30)	P-value
CPOT score	Day 1	1.9 ±.944	2.4 ± 1.16	0.073
	Day 2	2.86 ± 1.33	3.16 ± 1.48	0.414
	Day 3	2.4 ± 1.05	2.86 ± 1.33	0.135

Table III shows comparison of CPOT score of both groups in day 1, day 2 and day 3. In group A CPOT score was below 3 and in group B it was below 4.

Table IV: The requirement of rescue drug in both groups (n=60)

Variable		Group A (n=30)	Group B (n=30)	p- value
Requirement of rescue drug	Day 1	5 (16.7%)	4 (13.3%)	0.718^{ns}
	Day 2	7 (23.3%)	8 (26.7%)	0.766^{ns}
	Day 3	2 (6.7%)	3 (10%)	0.64^{ns}

Table IV shows comparison of both groups in relation to the mean requirement ofrescue drug. In the study period of 3 days in group A 5 patients in day 1, 7 patients in day 2 and 2 patients in day 3 required rescue drug and in group B 4 patients in day 1, 8 patients in day 2 and 3 patients in day 3 needed rescue drug.

Table V: The frequency of rescue drug in both groups (n=60)

Variable			Group A (n=30)	Group B (n=30)	p- value
Frequency of rescue drug	Day 1				
		Mean ± SD	2± 0.81	2.4±1.34	0.351^{ns}
		Range	1-3	1-4	
	Day 2				
		Mean ± SD	2.25± 1.28	2.71±1.49	0.787^{ns}
		Range	1-5	1-5	
	Day 3				
		Mean ± SD	2±1	2.5±2.12	0.732^{ns}
		Range	1-3	1-4	

Table V shows comparison of both groups in relation to the frequency of rescue drugin both groups. In the study period of 3 days in group A frequency of rescue drug was2±0.81 in day 1, 2.25±1.28 in day 2 and 2±1 in day 3 and in group B 2.4±1.34 inday 1, 2.71±1.49 in day 2 and 2.5±2.12 in day 3 needed rescue drug.

Table VI: The total daily dose of rescue drug in both groups (n-60)

Variable			Group A (n=30)	Group B (n=30)	p- value
Total daily dose of rescue drug	Day 1				
		Mean ± SD	5.2± 2.28	6.25±4.03	0.635^{ns}
		Range	3-9	3-12	
	Day 2				
		Mean ± SD	6.71± 4.11	7.13±3.64	0.841^{ns}
		Range	3-15	3-15	
	Day 3				
		Mean ± SD	6±4.24	6.33±4.93	0.943^{ns}
		Range	3-9	3-12	

Table VI shows comparison of both groups in relation to the total daily dose of rescuedrug in both groups. In the study period of 3 days in group A mean total daily dose ofrescue drug was lower than group B.

Table VII: Infusion duration of study drugs in both groups (n=60)

Variables		Group A (n=30)	Group B (n=30)	P-value
Infusion duration in hours	Mean± SD	47.63 ± 8.18	49.37±8.67	0.429^{ns}
	Range	21 -66	36 -66	

Table VII shows comparison of infusion duration of both groups. In group A mean infusion duration was 47.63 ± 8.18 hours and in group B was 49.37±8.67 hours.

Table VIII: Hemodynamic parameters of the patients (n=60)

Characteristics			Group A (n=30)	Group B (n=30)	P-value
Mean arterial pressure (mmHg)	Day 1	Mean±SD	81.4±6.55	80.93±6.54	0.784^{ns}
		Range	64-87	63-85	
	Day 2	Mean±SD	64.26±4.37	83.40±4.29	0.442^{ns}
		Range	63-87	64-87	
	Day 3	Mean±SD	85.1±3.42	83.43±4.32	0.104^{ns}
		Range	70-90	64-88	
Heart Rate (beats/min)	Day 1	Mean±SD	83.86±5.43	83.7±5.66	0.908^{ns}
		Range	58-95	55-90	
	Day 2	Mean±SD	82.8±4.93	81.06±5.76	0.216^{ns}
		Range	65-100	58-100	
	Day 3	Mean±SD	81.56±5.28	82.16±4.89	0.65^{ns}
		Range	68-105	65-100	

Table VIII shows comparison of hemodynamic parameters of both groups. In group Bmean MAP was lower than in group A. Mean heart rate in group B was lower than group A.

Table IX: Comparison of liver and renal function test in both study subject groups (n-60)

Variables		Group A (n=30)	Group B (n=30)	P-value
ALT(IU/L)	Mean±SD	41.34±2.69	40.43±1.9	0.139^{ns}
	Range	37.1-47.62	37.12-46.41	
AST (IU/L)	Mean±SD	42.37±3.68	41.7±2.51	0.457^{ns}
	Range	37.6-49.87	38.1-49.23	
Serum urea (mg/dl)	Mean±SD	25.90±2.96	25.70±2.81	0.604^{ns}
	Range	22.8-31.2	20.5-29.9	
Serum creatinine	Mean±SD	0.89±0.16	1.03±0.24	0.176^{ns}
	Range	0.7-1.2	0.7-1.5	

Table IX shows comparison of liver and renal function tests in both study subject groups. There was no significant difference in liver and renal function tests in both groups as p>0.05

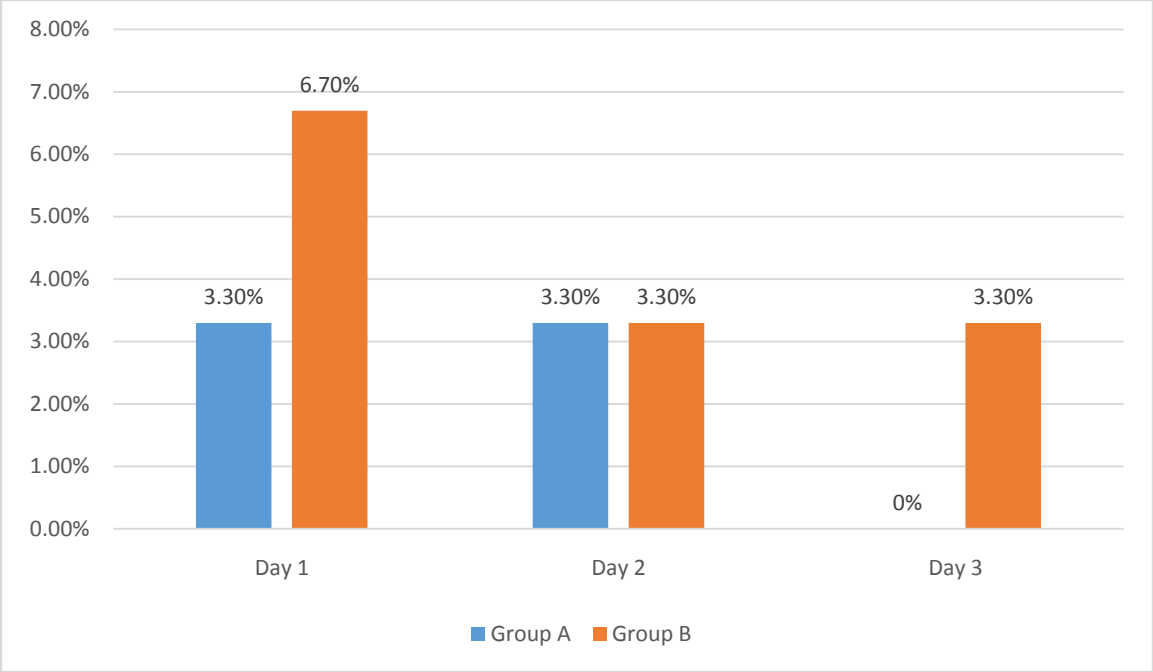

Figure II: Comparison of both groups according to hypotension (n= 60)

Hypotension of the patients of both groups is shown in Figure 6. Values wereexpressed as percentage. Hypotension was less observed in group A (2 patients) andin group B four patients developed hypotension.

IV. DISCUSSION

In this study, sedation level of mechanically ventilated patients in group A was intarget sedation level.Mean RAAS score was between -1 to -2 in remifenanil group. But in midazolam-fentanyl combination group patients were over sedated. Patients of this group were drowsy and were in light to moderate sedation. Mean RASS score was between -1 to -3. These findings of sedation level are similar for the midazolam-fentanyl group in relation to the findings of the study of Cevik. [13] But in their study sedation was assessed by Ramsay sedation scale (RS) and Sedation- agitation (SAS) scale. They found that patients of both groups were over sedated in the study period as patients of both remifenanil and fentanyl groups received midazolam infusion. But in this present study infusion of midazolam was only given in fentanyl group, but in remifentanil group only morphine boluses were given.

In this study, analgesia level of mechanically ventilated patients in group A was intarget analgesic level. Patients had mild or no pain.But in midazolam-fentanyl combination group patients Experienced moderate pain. Mean CPOT score was below 4. In this present study boluses of morphine which has analgesia properties were used in remifentanil group both conditions of inadequate sedation or analgesia, so the target CPOT score could.Moreover, Remifentanil has rapid onset of action of about 1 minute. Similar findings for target analgesia were found in a study conducted by Tanios where all patients were evaluated by Critical care observation tool (CPOT) for pain assessment. [14] In their study majority of the patients of analgesia-based sedation regime experienced no or mild pain and those who used hypnotic based sedation had moderate pain.

In this study rescue medications were allowed in case of inadequate sedation or analgesia. Bolus of morphine was used in group A and group B. But a greater number of patients of group B needed bolus doses of rescue medications to achieve target sedation and analgesia score. Frequncy of morphine and dose required were also higher in group B. Findings of Breen was similar with this study observation. [15] But the requirement of rescue medication was nine-fold more in hypnotic based sedation comparing with analgesia-based sedation.

In this study infusion time was 2 hours longer in midazolam-fentanyl group in relation toremifentanil group, previously in study conducted by Karabinis, it was observed that remifentanil infusion was longer in relation to hypnotic based sedation. [11]As their study population was patient with brain injury and they need sedation along with good control of pain for better outcome. But in this present study patient covered most of the disease spectrum, such as endocrine diseases, neurological disease, renal disease, respiratory disease, postsurgical disease, cardiovascular disease and obstetrics& gynecological disease.

Similar to the study finding of Muellejans, there was no significant differences between remifentanil and midazolam-fentanyl combination groups in relation to heart rate or mean arterial pressure. [16] There was acceptable hemodynamic stability in both groups. So,analgesia-based sedation regime using remifntanil could provide satisfactory degree of hemodynamic stability. But in this study, there was reduction in heart rate and mean arterial pressure in midazolam- fentanyl group.

Liver and renal function tests were also compared in both study subject groups. There was no significant difference in liver and renal function tests in both groups. Findings of liver and renal function tests were similar with the finding of Cevik. [13]Side effects of study medications were also observed and compared in this study. Hypotension occurred more in group B (6.7%) in comparison to group A (3.3%); Bradycardia occurred more in group B (6.7%) and it was 3.3% in group A. These findings were consistent with the findings of Breen. [10] This finding was observed as midazolam was not used in remifentanil group. On the other hand, patients of combination of midazolam and fentanyl group received continuous infusion of midazolam. Moreover, group A patients received drug infusion for shorter duration in comparison to group B and so that number of side effects was also less. So,side effects which are more common with midazolam like hypotension and bradycardia occurred more in group B.

In remifentanil group 10 patients in comparison to 7 patients of midazolam-fentanyl group were extubated. So, a greater number of patients of remifentanil group were extubated. But there was no significant difference of the number of patients being extubated, it can be because of the individual group size being small. Muellejanspublished literature with the similar findings of more patients extubated in remifentanil group as the drug has rapid onset and offset of action. [16]

So, the study reveals that remifentanil group had hemodynamic stability equivalent to midazolam-fentanyl combination group. And side effects were lower than the midazolam- fentanyl combination group. Moreover, regarding sedation and analgesia remifentanil as the single agent can be used effectively as traditional hypnotic based regime comprising of midazolam and fentanyl combination.

V. CONCLUSION

In this study, it was observed that remifentanil is effective for analgesia-based sedation in mechanically ventilated patients.

REFERENCE

[1]. Ostermann ME, Keenan SP, Seiferling RA, Sibbald WJ. Sedation in the intensive care unit: a systematic review. Jama. 2000 Mar 15;283(11):1451-9.

[2]. Grounds RM, Lalor JM, Lumley J, Royston D, Morgan M. Propofol infusion for sedation in the intensive care unit: preliminary report. British Medical Journal (Clinical research ed.). 1987 Feb 2;294(6569):397.

[3]. Pearson SD, Patel BK. Evolving targets for sedation during mechanical ventilation. Current opinion in critical care. 2020 Feb;26(1):47.

[4]. Olkkola KT, Ahonen J. Midazolam and other benzodiazepines. Modern anesthetics. 2008 Jan 1:335-60.

[5]. Obata Y, Adachi YU, Suzuki K, Itagaki T, Kato H, Satomoto M, Nakajima Y. The influence of differences in solvents and concentration on the efficacy of propofol at induction of anesthesia. Anesthesiology Research and Practice. 2016 Jan 21;2016.

[6]. Yu SB. Dexmedetomidine sedation in ICU. Korean journal of anesthesiology. 2012 May 1;62(5):405-11.

[7]. Battershill AJ, Keating GM. Remifentanil: a review of its analgesic and sedative use in the intensive care unit. Drugs. 2006 Feb; 66:365-85.

[8]. Scott LJ, Perry CM. Remifentanil: a review of its use during the induction and maintenance of general anaesthesia. Drugs. 2005 Sep; 65:1793-823.

[9]. Pitsiu M, Wilmer A, Bodenham A, Breen D, Bach V, Bonde J, Kessler P, Albrecht S, Fisher G, Kirkham A. Pharmacokinetics of remifentanil and its major metabolite, remifentanil acid, in ICU patients with renal impairment. British journal of anaesthesia. 2004 Apr 1;92(4):493-503.

[10]. Breen D, Wilmer A, Bodenham A, Bach V, Bonde J, Kessler P, Albrecht S, Shaikh S. Offset of pharmacodynamic effects and safety of remifentanil in intensive care unit patients with various degrees of renal impairment. Critical care. 2003 Feb; 8:1-0.

[11]. Karabinis A, Mandragos K, Stergiopoulos S, Komnos A, Soukup J, Speelberg B, Kirkham AJ. Safety and efficacy of analgesia-based sedation with remifentanil versus standard hypnotic-based regimens in intensive care unit patients with brain injuries: a randomised, controlled trial [ISRCTN50308308]. Critical care. 2004 Aug; 8:1-3.

[12]. Dahaba AA, Grabner T, Rehak PH, List WF, Metzler H. Remifentanil versus morphine analgesia and sedation for mechanically ventilated critically ill patients: a randomized double-blind study. The Journal of the American Society of Anesthesiologists. 2004 Sep 1;101(3):640-6.

[13]. Cevik F, Celik M, Clark PM, Macit C. Sedation and analgesia in intensive care: a comparison of fentanyl and remifentanil. Pain research and treatment. 2011;2011.

[14]. Tanios M, Nguyen HM, Park H, Mehta S, Epstein SK, Youssef F, Beltran A, Flores G, Sidhom R, Sehgal A, Leo J. Analgesia-first sedation in critically ill adults: a US pilot, randomized controlled trial. Journal of Critical Care. 2019 Oct 1; 53:107-13.

[15]. Breen D, Karabinis A, Malbrain M, Morais R, Albrecht S, Jarnvig IL, Parkinson P, Kirkham AJ. Decreased duration of mechanical ventilation when comparing analgesia-based sedation using remifentanil with standard hypnotic-based sedation for up to 10 days in intensive care unit patients: a randomised trial [ISRCTN47583497]. Critical care. 2005 Jun; 9:1-1.

[16]. Muellejans B, Matthey T, Scholpp J, Schill M. Sedation in the intensive care unit with remifentanil/propofol versus midazolam/fentanyl: a randomised, open-label, pharmacoeconomic trial. Critical Care. 2006 Jun;10(3):1-9.