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Safety and Efficacy of Dexmedetomidine, Ketofol, and Propofol for Sedation of Mechanically Ventilated Patients

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Abstract

Introduction: The Society of Critical Care Medicine recommended using non -benzodiazepine agents as propofol and dexmedetomidine for sedation of the critically ill patients in intensive care units.

Aims and Objectives: This study aimed to evaluate the safety and efficacy of ketofol, dexmedetomidine or propofol for sedation of postoperative mechanically ventilated patients in intensive care unit.

Materials and Methods: The study included ninety postoperative mechanically ventilated patients in the intensive care unit divided randomly into three equal groups.

Group A: 30 patients received ketofol an initial bolus dose (500 mcg/kg) of ketamine/propofol 1:1 (ketamine 8 mg/mL and propofol 8 mg/mL) followed by a maintenance dose of (10 mcg/kg/min). Group B: 30 patients received loading dose infusion of dexmedetomidin diluted in 0.9% sodium chloride 1 mcg/kg/h over 10 min followed by a maintenance infusion of 0.2-0.7 mcg/kg/h. Group C: 30 patients received propofol undiluted as an infusion of 1-3 mg/kg/h, after a loading dose infusion up to 1 mg/kg over 10 min.

Sedation level, bispectral index, systolic and diastolic blood pressure, heart rate, recovery time, complications (hypertension, hypotension, bradycardia).

Result: RAMSY sedation score was statistically significantly higher in group A than group B at the sixth and twelfth h; it was statistically significantly higher in group A than group C from the first to the twenty-fourth h and was statistically significantly higher in group B than group C at first, the sixth and eighteenth h. The recovery time was longer in group A compared to group B and C, and it was statistically significant, no complications recorded in the three groups.

Conclusion: Using ketofol, dexmedetomidine or propofol was effective in maintaining sedation without hemodynamic complications in postoperative mechanically ventilated patients in the intensive care unit.

Keywords: Sedation; Ketofol; Dexmedetomidine; Propofol

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Introduction

The critically ill patients in an intensive care unit are exposed to different noxious stimuli including postoperative pain, multiple venipuncture, invasive monitoring, and endotracheal intubation; therefore they are usually managed using a continuous-infusion of sedative [1]. It has been recommended by the Society of Critical Care Medicine (SCCM) to use non-benzodiazepine agents as propofol and dexmedetomidine for sedation regimen [2]. This change from benzodiazepines to non-benzodiazepines is

based on recent evidence reported that using benzodiazepine was an independent risk factor for the development of delirium, increased hospital Length of Stay (LOS) and increased 6-month mortality [3-7]. Alpha 2 agonist dexmedetomidine has sedative and analgesic effects and has been proved for ICU sedation for up to 24 h. It provides hemodynamic stability without depressing respiration. It produces mild cognitive impairment allowing easy communication between the healthcare provider and the patient in the ICU. It also has the advantages of reducing the costs of ICU stay and more natural liberation from mechanical ventilation [8-10]. It has been reported that intravenous ketamine/propofol combination (ketofol) can be used for sedation for 24 h [11]. This is based on the finding that propofol is recommended for the short-term (<24 h) treatment of anxiety in the critically ill adult patients and continuous infusion doses of ketamine have also been described for 24 h, so ketofol was expected to be given safely as a continuous infusion for 24 h [12], with the advantages of increasing their safety and efficacy and decreases their side effects [13].

In a study by Hamimy et al. continuous intravenous infusion of ketofol provided adequate and safe short-term sedation (less than 24 h) for critically ill patients in the intensive care units, rapid recovery without significant complications but because of the small size of their case series further studies with more significant number of patients were recommended to confirm their finding [14].

This study aimed to evaluate the safety and efficacy of using ketofol compared to dexmedetomidine or propofol for sedation of postoperative patients who required mechanical ventilation in the intensive care unit.

Materials and Methods

This study was conducted in the Surgical Intensive Care Unit (SICU) of Beni-Suef University hospital; the study was registered at PACRT (trial registration number 201803003203136) after obtaining approval from the anesthesia department and the local committee of ethics and research (The FM-BSU REC) and obtaining consents from the patients or their guardians. This study was performed from 21 November 2015 to 21 November 2017.

The study included ninety postoperative adult patients of both sex (aged 18-65 years old) who required close monitoring and mechanical ventilation and sedation for 24 h after major surgery, excluding pregnant females, history of epilepsy and patients with increased intracranial tension, major renal, hepatic or cardiac diseases, neurosurgical operations or having allergies to the studied drugs. On arrival to the SICU the patients were connected to mechanical ventilator (initial sitting were SIMV mode, FiO_2 40%, PEEP 5-8 cm H_2O, pressure support 10-15 Cm H_2O), monitoring were applied (5 leads ECG, pulse oximetry, capnography, invasive and noninvasive arterial blood pressure, and central venous pressure were monitored), BIS electrodes were applied to the forehead. 12 leads ECG, chest X-ray were done; a blood sample was taken for complete blood count, biochemistry and arterial blood gas analysis. The patients were randomly divided into three equal groups according to closed, opaque envelop technique (30 patients each):

Group A: 30 patients received ketofol an initial bolus dose (500 mcg/kg) of ketamine/propofol 1:1 (ketamine 8 mg/ml and propofol 8 mg/mL followed by a maintenance dose of (10 mcg/kg/min) [14].

Group B: 30 patients received loading dose infusion of dexmedetomidine (precedex, Hospira inc lake forest, IL60045 US) diluted in 0.9% sodium chloride 1 mcg/kg/h over 10 min followed by a maintenance infusion of 0.2-0.7 mcg/kg/h [15].

Group C: 30 patients received propofol (diprivan;Fresenius Kabi Astaria GmbH-A8005Gra kz, Austaria) undiluted as an infusion of 1-3 mg/kg/h, after a loading dose infusion up to 1 mg/kg over 10 min.

The following data were collected and recorded by SICU staff unaware of the study protocol

1. Demographic data (age, sex, weight) and types of surgeries.
2. Degree of sedation was recorded hourly for 24 h using the Ramsay sedation score (16) and continuously using the bispectral index, and the sedation level was maintained at RSS>2 by adjustment of the drug infusion rate, as a primary outcome.
3. Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Heart Rate (HR).
4. Recovery time: the time required for the patient to regain the conscious level before sedation) after discontinuing sedation [16].
5. Complications including hypotension which is defined as (systolic blood pressure less than 90 mmHg), hypertension which is defined as systolic blood pressure more than 160 mmHg, bradycardia (heart rate less than 60 beats/minute), and tachycardia (heart rate more than 90 beats/minute) were also recorded. Hypotension was managed by lowering the infusion rate of sedation and IV bolus of crystalloid fluid; hypertensive events were achieved by increasing the sedation infusion rate till stabilizing the blood pressure then the infusion rate was adjusted according to the study protocol.

Inadequate analgesia was expected if the patient experienced tachycardia or hypertension>20% from the baseline reading in spite of adequate sedation level as indicated by BIS value, so fentanyl (25-50 µg IV bolus) was given.

Statistical analysis

Sample size

After a pilot study with five patients in each group, the minimum detectable difference in RSS between groups was 0.8, and a standard deviation of residuals was 0.7. Accordingly, the calculated

minimum sample size was 24 patients in each group with 95% power and α level was 0.05 using F-test (ANOVA), Biostatstics, version3.01.The number was increased to 30 patients in each group in case of the drop in any case.

Statistical methods

All statistical calculations were done using computer programs Microsoft Excel (Microsoft Corporation, NY, USA) & SPSS (Statistical Package for the social science) statistical programs (SPSS Inc., Chicago, IL, USA). Data were statistically described in terms of mean ± standard deviation (SD), median (range) or number (percentage) as appropriate.

Inferential analyses were done for quantitative variables using paired T-test or one way ANOVA. P-values less than 0.05 were considered significant and p values less than 0.01 were considered highly significant.

Results

All cases completed the study, **Figure 1.**

Table 1 showed the types of surgeries

No statistically significant differences in the demographic data between the studied groups (p value>0.05); **(Table 2).**

Systolic Blood Pressure (SBP), diastolic Blood Pressure (DBP) and Heart Rate (HR) were recorded before starting sedation, then after starting sedation by 30 min, then hourly for 24 h, but for statistical analysis the data were averaged and recorded at 6 h interval.

The heart rate was higher in group A than group B and C before starting sedation, but it was not statistically significant (p>0.05), the heart rate was statistically significantly higher in group A than both group B and C 30 min after starting sedation and at sixth, twelfth, eighteenth and twenty-fourth h (p<0.001), it was also statistically significantly higher in group C than group B 30 min after starting sedation and at sixth, twelfth, eighteenth and twenty-fourth h (p<0.001) **(Table 3)**.

The systolic arterial blood pressure was statistically significantly higher in group A than both group B and C 30 min after starting sedation, and at sixth, twelfth, eighteenth and twenty-fourth h,

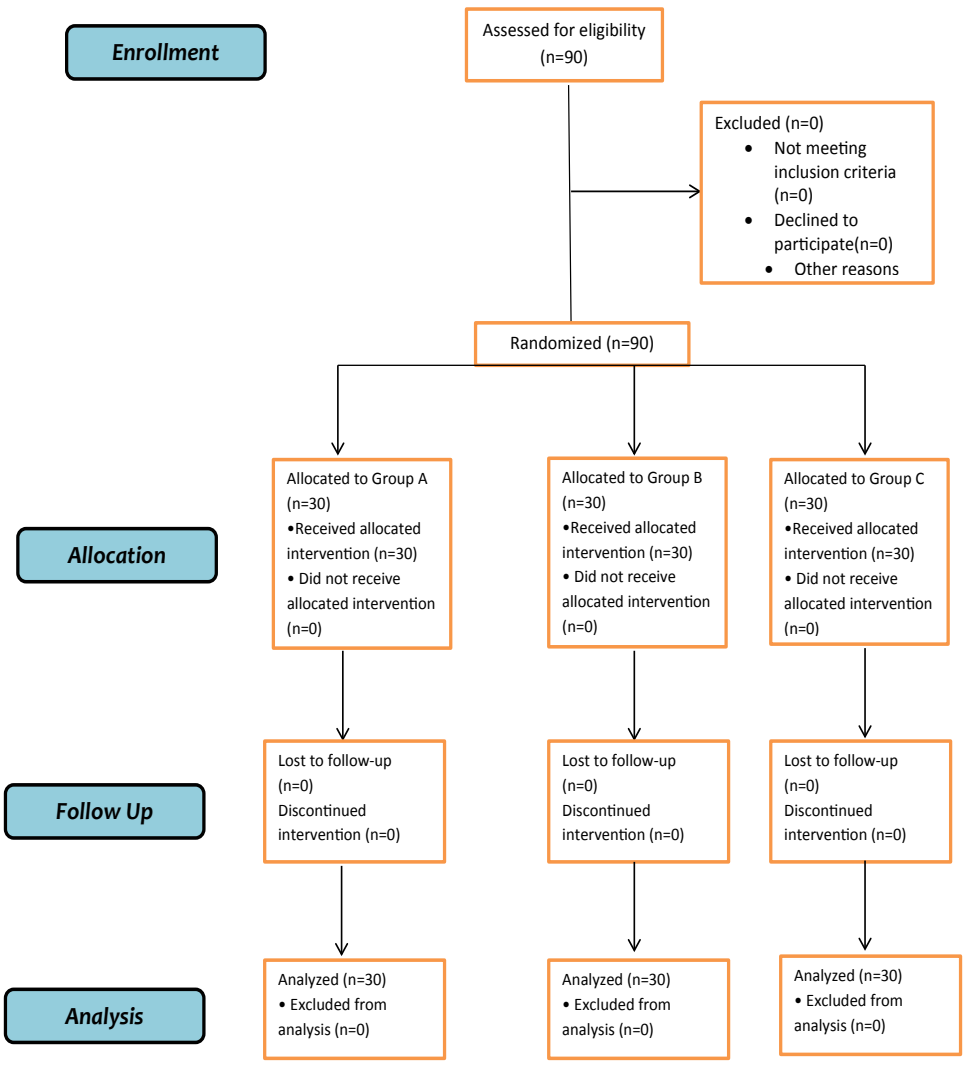

Figure 1 Consort flow participant diagram.

Table 1 Types of surgeries.
Group A (Ketofol group), Group B (Dexmedetomidine group), Group C (Propofol group).
Data are presented as numbers (%)

Types of surgeries (no %)	Group A (n=30)	Group B (n=30)	Group C (n=30)
Cesarean hysterectomy	8 (26.6)	9 (30)	8 (26.6)
Radical cystectomy	5 (16.6)	3 (10)	5 (16.6)
Abdominal Exploration	7 (23.3)	8 (26.6)	4 (13.3)
Amputation	8 (26.6)	5 (16.6)	4 (13.3)
Embolectomy	0 (0)	2 (6.6)	3 (10)
Fixation of fractured femur	2 (6.6)	1 (3.3)	3 (10)
Fixation of cervical spine	0 (0)	2 (6.6)	2 (6.6)
Fixation of dorsal spine	0 (0)	0 (0)	1 (3.3)

Table 2 Demographic data of the three groups.
Group A (Ketofol group), Group B (Dexmedetomidine group), Group C (Propofol group).
Data were presented as mean ± SD and number (percentage), p<0.05 is considered significant

Variable	Group A (n=30)	Group B (n=30)	Group C (n=30)	p value
Age (year)	34.6 ± 18.0	35.5 ± 14.7	40.2 ± 13.4	0.329
Weight (kg)	67.7 ± 5.0	66.1 ± 7.7	68.5 ± 5.4	0.303
Sex, no. (%)				0.868
• Male	18 (60)	20 (66.7)	19 (63.3)	
• Female	12 (40)	10 (33.3)	11 (36.7)	

Table 3 Heart rate (Bpm).
Group A (Ketofol group), Group B (Dexmedetomidine group), Group C (Propofol group).
Data were presented as mean ± SD.
p value<0.05 were considered significant and P values<0.01 were considered highly significant.
p1: p value of comparison between group A and B.
p2: p value of comparison between group A and C.
p3: p value of comparison between group B and C.

Time	Group A (n=30)	Group B (n=30)	Group C (n=30)	p value
Before sedation	106.5 ± 8.1	103.2 ± 11.2	101.1 ± 23.9	p_1=0.419
				P_2=0.192
				p_3=0.616
30 min after sedation	90.4 ± 1.7	66.2 ± 1.3	84.5 ± 1.3	p_1<0.001
				p_2<0.001
				p_3<0.001
6th h after sedation	91.1 ± 1.6	63.6 ± 1.2	83.3 ± 1.2	p_1<0.001
				p_2<0.001
				p_3<0.001
12th h after sedation	91.1 ± 1.9	62.8. ± 1.8	85.7 ± 1.6	p_1<0.001
				p_2<0.001
				p_3<0.001
18th h after sedation	92.3 ± 2.3	61.1 ± 1.6	82.2 ± 1.7	p_1<0.001
				p_2<0.001
				p_3<0.001
24th h after sedation	91.4 ± 1.5	62.3 ± 1.3	82.6 ± 1.6	p_1<0.001
				p_2<0.001
				p_3<0.001

(p<0.001), it was also statistically significantly higher in group B than C 30 min after starting sedation and at sixth, twelfth, eighteenth and twenty-fourth h (p<0.001) **(Table 4)**.

The Diastolic Blood Pressure (DBP) was statistically significantly higher in group A than group B and C from the first to the 24th h, DBP was statistically significantly higher in group B than C 30 min after starting sedation and at the sixth, twelfth, eighteenth and twenty-fourth h (p<0.001) **(Table 5)**.

BIS value was statistically significantly higher in group A than group B at sixth h only (p<0.01). It was statistically significantly

Table 4 Systolic arterial blood pressure (mmHg).
Group A (Ketofol group), Group B (Dexmedetomidine group), Group C (Propofol group).
Data were presented as mean ± SD.
p values less than 0.05 were considered significant and P values less than 0.01 were considered highly significant.
p1: p value of comparison between group A and B.
p2: p value of comparison between group A and C.
p3: p value of comparison between group B and C.

Time	Group A (n=30)	Group B (n=30)	Group C (n=30)	p value
Before sedation	135.4 ± 4.3	134.7 ± 4.7	136 ± 6.5	p1=0.26
				p2=0.33
				p3=0.18
30 min after sedation	124.3 ± 4.2	114.6 ± 3.6	103.6 ± 4.1	p1=0.001
				p2=0.001
				p3=0.001
6th h after sedation	124.5 ± 6.2	111.5 ± 4.8	102.8 ± 2.2	p1=0.001
				p2=0.001
				p3=0.001
12th h after sedation	125.8 ± 6.4	114.2 ± 3.5	103.9 ± 2.8	p1=0.001
				p2=0.001
				p3=0.001
18th h after sedation	126.2 ± 4.7	112.9 ± 3.7	103.1 ± 3.9	p1=0.001
				p2=0.001
				p3=0.001
24th h after sedation	127.4 ± 5.6	113.1 ± 4.5	104.5 ± 4.3	p1=0.001
				p2=0.001
				p3=0.001

Table 5 Diastolic arterial blood pressure (mmHg).
Group A (Ketofol group), Group B (Dexmedetomidine group), Group C (Propofol group).
Data were presented as mean ± SD.
p values less than 0.05 were considered significant and P values less than 0.01 were considered highly significant.
p1: p value of comparison between group A and B.
p2: p value of comparison between group A and C.
p3: p value of comparison between group B and C.

Time	Group A (n=30)	Group B (n=30)	Group C (n=30)	p value
Before sedation	79.7 ± 1.3	80.3 ± 3	79.8 ± 2	p1=0.16
				p2=0.33
				p3=0.27
30 min after sedation	74.7 ± 1.3	69.5 ± 1	58.2 ± 0.8	p1=0.001
				p2=0.001
				p3=0.001
6th h after sedation	75.8 ± 1.2	68 ± 0.8	57.1 ± 0.8	p1=0.001
				p2=0.001
				p3=0.001
12th h after sedation	73.5 ± 1.1	65.5 ± 1.3	58.4 ± 1.4	p1=0.001
				p2=0.001
				p3=0.001
18th h after sedation	73.4 ± 1.2	62.1 ± 0.9	58.4 ± 1.3	p1=0.001
				p2=0.001
				p3=0.001
24th h after sedation	75.5 ± 0.8	63 ± 0.8	58.8 ± 1	p1=0.001
				p2=0.001
				p3=0.001

higher in group A than group C at first and eighteenth h ($p<0.01$), and was statistically significantly higher in group B than group C from the first to 24 h ($p<0.01$) **(Table 6)**.

RAMSY sedation score was statistically significantly higher in group A than group B at sixth and twelfth h, it was statistically significantly higher in group A than group C in the first, sixth and eighteenth h, it was statistically significantly higher in group B

Table 6 Bispectral index (BIS).
Group A (Ketofol group), Group B (Dexmedetomidine group), Group C (Propofol group).
Data were presented as mean ± SD.
p values<0.05 were considered significant and P values<0.01 were considered highly significant.
p1: p value of comparison between group A and B.
p2: p value of comparison between group A and C.
p3: p value of comparison between group B and C.

BIS	Group A (n=30)	Group B (n=30)	Group C (n=30)	p-value
1st h	76.6 ± 2.7	76.8 ± 3.9	72.7 ± 3.2	p1=0.846 p2=0.001 p3=0.001
6th h	74.8 ± 3.1	76.7 ± 3.5	73.2 ± 4.0	p1=0.037 p2=0.090 p3=0.001
12th h	74.7 ± 3.5	76.3 ± 3.0	73.6 ± 3.5	p1=0.059 p2=0.210 p3=0.002
18th h	75.1 ± 3.3	76.2 ± 3.4	72.3 ± 3.4	p1=0.209 p2=0.002 p3=0.001
24th h	74.4 ± 2.9	75.5 ± 2.8	72.7 ± 4.2	p1=0.196 p2=0.064 p3=0.002

Table 7 Ramsay sedation score.
Group A (Ketofol group), Group B (Dexmedetomidine group), Group C (Propofol group).
Data were presented as median (range).
p values<0.05 were considered significant and P values < 0.01 were considered highly significant.
p1: p value of comparison between group A and B.
p2: p value of comparison between group A and C.
p3: p value of comparison between group B and C.

RAMSY scoring system	Group A (n=30)	Group B (n=30)	Group C (n=30)	p value
1st h	3 (2-4)	3 (2-4)	3 (2-5)	p1=0.397 p2=0.0001 p3=0.0001
6th h	3 (2-4)	3 (2-4)	3 (3-5)	p1=0.022 p2=0.028 p3=0.003
12th h	3 (2-4)	3 (2-4)	3 (3-5)	p1=0.006 p2=0.179 p3=0.001
18th h	3 (2-4)	3 (2-4)	3 (3-5)	p1=0.306 p2=0.0009 p3=0.0009
24th h	3 (2-4)	3 (2-4)	3 (3-5)	p1=0.085 p2=0.120 p3=0.011

than group C from the first to twenty-fourth h **(Table 7).**

The recovery time was longer in group A compared to group B and C, and it was statistically significant (p<0.05) **(Table 8)**.

The mean administered dosages of fentanyl was 382.3 ± 9.7 µg, 349.8 ± 7.5 µg, 439.7 ± 12.3 µg for groups A-C respectively, it was statistically significantly higher in group C than group A and B group (p<0.001), and it was statistically significantly higher in group A than in B group (p<0.001) **(Table 9)**.

Discussion

The current study showed that infusion of ketofol, dexmedetomidine or propofol was effective for sedation of mechanically ventilated patients in SICU as detected by RSS which is maintained in the range of 2-4 for the patients who were sedated by ketofol or dexmedetomidine and 2-5 for the patients who were sedated by propofol without causing hemodynamic complications. Dexmedetomidine group required less fentanyl for postoperative analgesia.

Table 8 Recovery time (min).
Group A (Ketofol group), Group B (Dexmedetomidine group), Group C (Propofol group).
Data were presented as mean ± SD.
p values<0.05 were considered significant and P values<0.01 were considered highly significant.
p1: p value of comparison between group A and B.
p2: p value of comparison between group A and C.
p3: p value of comparison between group B and C.

	Group A (n=30)	Group B (n=30)	Group C (n=30)	p value
Recovery time (min.)	35.8 ± 14.4	29.5 ± 10.9	27.7 ± 8.6	p1=0.038 p2=0.038 p3=0.541

Table 9 Fentanyl requirement (µg).
Group A (Ketofol group), Group B (Dexmedetomidine group), Group C (Propofol group).
Data were presented as mean ± SD.
p values<0.05 were considered significant and P values<0.01 were considered highly significant.
p1: p value of comparison between group A and B.
p2: p value of comparison between group A and C.
p3: p value of comparison between group B and C.

	Group A (n=30)	Group B (n=30)	Group C (n=30)	P value
Fentanyl requirement (µg)	382.3 ± 9.7	349.8 ± 7.5	439.7 ± 12.3	p1<0.001 p2<0.001 p3<0.001

There are few available data in the scientific literature for using ketofol for sedating the patients in ICUs but there are several trials used ketofol for procedural sedation. The result of this study coincides with those of the study which was performed by Hamimy et al. [14]. They concluded that using ketofol for sedating the mechanically ventilated patients was effective in maintaining Ramsay sedation score of 4 without hemodynamic instability.

Willman [17] and Andolfatto [18] concluded that none of the patients developed hypotension when ketofol was administrated in a mean dose of (0.75 mg/kg of ketamine and 0.75 mg/ kg of propofol) but they reported in another study that only 1 patient out of 728 patients became hypotensive when ketofol was used for PSA for orthopedic procedures. Dal et al. [19] concluded that ketofol was effective and safe for sedation during endobronchial ultrasound-guided needle aspiration procedure.

Ghadami et al. [20] reported that quality of sedation, the total dose of the drug and respiratory and hemodynamic parameters were comparable when using two different ratios of ketofol in 60 pediatric patients scheduled for lumbar puncture or bone marrow aspiration. David et al. [21] did not report a significant difference in respiratory depression between 98 adults and 93 children.

Tosun et al. [22] demonstrated that ketofol was useful for sedation and providing hemodynamic stability in pediatric patients who underwent upper GIE procedures.

On the other hand, Loh et al. [23] reported that fewer patients who were given ketofol had a significant hemodynamic compromise, and required active interventions using fluid or vasopressor. They explained their results by the opposite effect of ketamine and propofol on the autonomic nervous system, as ketamine is sympathomimetic, but propofol lessens this effect.

One study was done by Venn et al. [24] which included 20 adult patients who required at least 8 h of postoperative mechanical ventilation, the patients who were sedated by dexmedetomidine significantly needed less alfentanil (2.5 *vs.* 0.8 $mg.h^{-1}$) than those sedated by propofol. RSS for propofol was 5 [4,5], and for dexmedetomidine, RSS was 5 [4-6]. In the current study, RSS was 2-4 for dexmedetomidine and 2-5 for the patients who were sedated by propofol; the difference between this study and the study of Venn et al. may be explained by different time for assessing the BIS value as this study was for 24 h and the study of Venn et al. [24] was for 8 h, also due to different number of the patients between the two studies.

In a study by Prerana et al. [25] that included thirty patients who required postoperative mechanical ventilation and sedation; 15 patients received dexmedetomidine, and 15 patients received propofol. The mean pulse-rate, respiratory rate, blood pressure between the groups was not statistically significant. The mean RSS was between 2-4 and 2-3 for dexmedetomidine and propofol groups respectively.

In this study, Ramsay sedation score was 2-4 and 2-5 for dexmedetomidine group and propofol group respectively. These results were not in line with the study by Corbett et al. [26] they titrated dexmedetomidine or propofol to a Ramsay sedation score of 3–4.

Demiraran et al. [27] did not find a difference in HR, mean arterial pressure, or recovery time in a prospective trial of 50 patients underwent upper endoscopy sedated with dexmedetomidine or midazolam.

Stephan et al. [28] reported that ICU patients receiving prolonged mechanical ventilation, dexmedetomidine was comparable

to midazolam and propofol in maintaining light to moderate sedation. In the current study the recovery time was 35.8 ± 14.4 min for the patients sedated by ketofol 29.5 ± 10.9 min for the patients sedated by dexmedetomidine and it was 27.7 ± 8.6 min for the patients who were sedated by propofol, while in the study of Hamimy et al. [14] the median recovery time was 30 min (range 18–60 min) and in the study of Andolfatto et al. [17] the median recovery time was 14 min (range 3–50 min). The different number of patients may explain the difference between this study and other studies, and they used ketofol while in this study included three groups of patients sedated by ketofol, dexmedetomidine or propofol, and Andolfatto et al. [17] used ketofol for procedural sedation.

In this study, the patients sedated by dexmedetomidine required less fentanyl than patients sedated by ketofol or propofol. This was also reported by Vinit et al. [29].

Conclusion

This study concluded that using ketofol, dexmedetomidine or propofol for sedation of postoperative intubated and mechanically ventilated patients in the surgical ICU for 24 h was effective in maintaining Ramsay sedation score in the range of 2-4 for the patients who were sedated by ketofol or dexmedetomidine and 2-5 for the patients who were sedated by propofol without causing hemodynamic instability.

Limitations of the Study

More studies are recommended for the longer duration of mechanical ventilation.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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