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Dexmedetomedine versus Standard Sedatives in Weaning from Mechanical Ventilation

Nabila M. Fahmy, Hatem S. Abdel Hamid, Amal H. Rabie, Hany M. Salib, Ayman E. Abdellatif

Department of Anesthesiology & Intensive Care Medicine, Faculty of Medicine Ain Shams University

Corresponding author: Ayman E. Abdellatif; **Mobile:** 01060498594, **Email:** aymanelsaid2312@gmail.com

ABSTRACT

Background: Sedation in the intensive care unit Patients is assumed to reduce discomfort from care interventions, increase tolerance of mechanical ventilation, prevent accidental removal of instrumentation, and reduce metabolic demands during cardiovascular and respiratory instability. **Aim of the Work:** The aim of the work was to evaluate the use of dexmedetomedine as a sedative to facilitate weaning from mechanical ventilation and extubation, so decrease the incidence of reintubation, ventilator complications and decrease the ICU cost and stay. **Patients and Methods:** This was a controlled randomized prospective clinical trial carried out at Ain-Shams University Hospitals. After approval of institutional ethical committee, the study included 90 adult postoperative patients and requiring postoperative mechanical ventilation in the surgical ICU for maximum duration of 48 hours postoperatively. **Results:** As regard to time to extubation, results of the current study showed a highly statistically significant difference between three groups regarding time to extubation (hr) when p-value was < 0.001. **Conclusion:** dexmedetomidine has clinically relevant benefits compared to midazolam and propofol in facilitating extubation because of its shorter time to extubation, more hemodynamic stability, easy arousability and lack of respiratory depression; hence, it can be used as an effective, and safe sedative agent to facilitate extubation in ICUs and decreasing ICU length of stay.

Key words: Dexmedetomedine, Standard Sedatives, Mechanical Ventilation, Weaning

INTRODUCTION

Pain, agitation and delirium commonly occur in critically ill patients, with potential consequences that necessitate treatment with analgesic, sedative and antipsychotic medications. Over the last 15 years, considerable evidence has accumulated demonstrating that both choice of agent and how we use these drugs can significantly impact clinically relevant patient outcomes. This, in turn, has influenced recent pain, agitation and delirium guidelines [(1)].

Patients requiring mechanical ventilation are typically having significant anxiety and pain [(2)]. These patients require sedation to tolerate the tracheal tube and the ventilator, to suppress cough, to prevent respiratory fighting during intensive care procedures and to prevent psychological complications associated with pain and anxiety. An ideal sedative agent should allow for rapid modification of the sedation level by titration of doses, no depressant effects on the cardiovascular or respiratory systems, cheap, have short duration without cumulative effects, and allow rapid recovery of effective spontaneous respiration after stopping the infusion [(3)].

The pharmacologic control of analgesia and sedation is nearly a routine in everyday practice in intensive care units (ICUs) worldwide, especially in the management of symptoms of mechanically ventilated patients [(1)].

Sedative medications are often provided for comfort in mechanically ventilated patient but have been associated with harm, including occurrence of delirium, ventilator-associated pneumonia (VAP), and prolonged mechanical ventilation [(4)].

The process of weaning from mechanical ventilation is central to the management of critically ill patients. It is a very complex and difficult task. Attention should be paid to wean off the ventilator as quickly as possible after the conditions that warranted placing the patient on the ventilator begin to resolve and stabilize [(5)]. Delayed or unnecessarily prolonged weaning increases length of intensive care unit (ICU) stay, health-care cost, decreases the ICU bed availability and adversely affects patient outcome [(6)].

Dexmedetomidine is a selective alpha-2-adrenoceptor agonist. It exerts both sedative and analgesic effects via mechanisms different from other sedatives such as midazolam and propofol, and provides sedation characterized by prompt response to stimuli with no respiratory depression [(7)]. Therefore does not interfere with weaning from mechanical ventilation. Because of this characteristic, infusions of dexmedetomidine can be continued after extubation without the risk of respiratory failure, a complication that can occur with propofol, lorazepam, and midazolam [(8)].

AIM OF THE WORK

The aim of the work was to evaluate the use of dexmedetomedine as a sedative to facilitate weaning from mechanical ventilation and extubation, so decrease the incidence of reintubation, ventilator complications and decrease the ICU cost and stay.

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PATIENTS AND METHODS

This controlled randomized prospective clinical trial was carried out at Ain-Shams University Hospitals.

After approval of institutional ethical committee, the study was conducted on 90 adult postoperative patients and requiring postoperative mechanical ventilation in the surgical ICU for maximum duration of 48 hours postoperatively.

Inclusion Criteria: Male and female patients aging ≥ 18 years and ≤ 60 years of age. Patients in need for mechanical ventilation and sedation for 24 to 48 hours in the surgical ICU after prolonged major pelvi-abdominal operations which are radical cystectomy, Whipple's operation, partial gastrectomy and total colectomy.

The main exclusion criteria: Age < 18 years >60 years. Patients with liver (Childs Pugh class-C) or renal failure. Severe neurological disorders like head trauma, brain tumors, brain edama and known epileptic on anticonvulsants. Heart diseases like Recent myocardial infarction, Heart block, heart rate <50 beats/min. Systolic blood pressure <90 mm Hg despite continuous infusions of vasopressors. Patient on antipsychotic or sedatives. Pregnant/lactating females. Patients allergic to midazolam, dexmedetomidine or propofol.

Methodology:

Preoperatively:

Routine pre-operative assessment was done to all patients including: history, clinical examination, laboratory investigations (complete blood picture, liver function tests, kidney function tests, prothrombin time and partial thromboplastin time) and electrocardiogram were done for all patients, and other investigations were done according to the medical condition, from which the included patients will be selected retrospectively.

In the intensive care unit:

The patients arrived to the ICU intubated, and were immediately artificially ventilated with synchronized intermittent mandatory ventilation (SIMV) with pressure support mode. When the patients could open their eyes on command, they were allocated into three groups, 30 patients in each group according to the drugs used, by the single blind technique as the treating physician only was aware of the drugs given, group 'D' received IV dexmedetomidine infusion, group 'P' received IV Propofol infusion and group "M" received iv midazolam infusion whilst being mechanically ventilated. No muscle relaxants were given during the study period.

Dexmedetomidine (Precedex, Hospira, Lake Forest, USA) was supplied in 2-ml ampoules at a concentration of 100 µg/ml. It was diluted with normal saline to a concentration of 4 µg/ml. Group 'D' received a loading infusion dose of dexmedetomidine 2.5 µg/kg/h over 10 minutes followed by maintenance infusion at a rate of 0.2-0.5 µg/kg/h into a peripheral vein, with the dosage adjusted to achieve the desired level of sedation (Richmond Agitation Sedation Score -2 to 0).

The second group 'P' received propofol (Propofol, Fresenies Kapi, Austria) undiluted as a bolus dose of 1 mg/kg initially, followed by an infusion of 1-2 mg/kg/h, with the dosage adjusted to achieve the desired level of sedation (RASS -2 to 0). The degree of sedation was measured by ICU residents and recorded using the Richmond agitation sedation score (RASS) every 6 hours.

The third group "M" received midazolam loading dose 10-15mcg/kg (dose range from 0.5-4mg) slow IV injection or infusion over several minutes, repeat q5-15 min PRN. Maintenance: initial 20-100mcg/kg/hr infusion. The degree of sedation was measured by ICU residents and recorded using the Richmond agitation sedation score (RASS) every 6 hours.

Table (1): Richmond Agitation-Sedation Scale (RASS) [9].

Description	Term	Score
Overtly combative or violent; immediate danger to staff	Combative	+ 4
Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff	Very agitated	+ 3
Frequent nonpurposeful movement or patient-ventilator dyssynchrony	Agitated	+ 2
Anxious or apprehensive but movements not aggressive or vigorous	Restless	+ 1
Alert and calm	0	
Not fully alert, but has sustained (> 10 seconds) awakening, with eye contact, to voice	Drowsy	- 1
Briefly (< 10 seconds) awakens with eye contact to voice	Light sedation	- 2
Any movement (but no eye contact) to voice	Moderate sedation	- 3
No response to voice, but any movement to physical stimulation	Deep sedation	- 4
No response to voice or physical stimulation	Unarousable	- 5

The dose of both drugs was adjusted by varying the dose by 10% increase or decrease in the infusion rate in order to maintain the level of sedation

within the range considered adequate. Patients were ventilated mechanically with oxygen enriched air to achieve acceptable blood gases as well as end-tidal CO2. Heart rate (HR) and mean arterial blood pressure (MAP) were monitored continuously and recorded hourly, and documented every 6 hours.

A daily awakening trial was performed. A Daily Awakening Trial determines a patient's minimum level of sedation and identifies the minimum effective dose. Once the patient is awake and responsive, an accurate sedation, pain, and delirium assessment can be obtained, as well as a spontaneous breathing trial of the ventilated patient.

The sedative infusion was discontinued, in preparation for extubation. Extubation was undertaken when there was no evidence of bleeding and the patient was alert, hemodynamically stable, normothermic and with an arterial oxygen tension ≥70 mmHg on an inspired oxygen concentration ≤ 35% and had positive end-expiratory pressure < 5 cm H2O, spontaneous respiration had been established with pressure support < 10 cm H2O, a tidal volume of > 6 ml/ kg and respiratory rate ≥10 breaths/min but <20 breaths/min.

Monitoring of pain was done by: The Critical care Pain Observation Tool (CPOT) [10]: Analgesics were given if CPOT of the patient is >3. Frequency of analgesic injections was recorded. Total analgesic requirements in the ICU were recorded. Analgesia was provided by giving Nalbufin 10 – 20 mg i.v.or i.m, this dose was repeated every 6 hours as needed with maximum total daily dose of 100 mg. Demographic data recording for the patients (age, gender, ASA classification and body weight). Heart rate, mean arterial blood pressure central venous pressure and oxygen saturation were monitored and recorded hourly and documented every 6 hours. Extubation time (the time from cessation of sedative agent to extubation event) was recorded. Extubation time was considered the primary end point of the study while the vital data (heart rate, mean arterial blood pressure and oxygen saturation) was considered the secondary end point. Incidence of complications (e.g. bradycardia, tachyarrhythmia) was recorded and treated accordingly. Time of ICU length of stay was recorded. Time frame was recorded for each patient; from the patient's entry to the ICU till discharge. Observation and recording for occurrence of any side effects of the used drugs (e.g. hypotension) was recorded. Patients who maintain effective spontaneous breathing without any mechanical assistance for 24 h after extubation will be considered as successfully weaned and those who will not, will be excluded from the study and will be considered as extubation failure.

Statistics: Statistical presentation and analysis of the present study was conducted, using the mean, standard Deviation, paired student t-test, Analysis of variance [ANOVA] and chi-square tests by SPSS V20.

Analysis of variance [ANOVA] tests.

According to the computer program SPSS for Windows. ANOVA test was used for comparison among different times in the same group in quantitative data: >0.05 Non significant. <0.05* significant. <0.001** High significant.

RESULTS

1- As regard the demographic data; the age group, sex and BMI, did not differ statistically between the three groups tested (Tables 2,3,4).

Table (2): Comparison between three groups regarding sex.

Sex		Groups							
		Dexmedetomedine		Propofol		Midazolam		Total	
		N	%	N	%	N	%	N	%
Female		12	40.0	14	46.7	11	36.7	37	41.1
Male		18	60.0	16	53.3	19	63.3	53	58.9
Total		30	100.0	30	100.0	30	100.0	90	100.0
Chi-square	X2	0.643							
	P-value	0.725							

This table shows non statistically significant deference between three groups regarding sex when p-value was >0.05.

Table (3): Comparison between the three groups regarding Age.

Groups	Age						ANOVA	
	Range			Mean	±	SD	f	P-value
Dexmedetomedine	37	-	55	45.77	±	5.02	0.507	0.604
Propofol	31	-	55	44.37	±	5.92		
Midazolam	35	-	58	45.38	±	5.70		

This table shows non statistically significant deference between three groups regarding Age when p-value was >0.05.

Table (4): Comparison between the three groups regarding BMI.

Groups	BMI						ANOVA	
	Range			Mean	±	SD	f	P-value
Dexmedetomedine	24	-	36.5	30.87	±	2.94	2.299	0.106
Propofol	22	-	37	29.10	±	3.87		
Midazolam	24	-	37	30.15	±	2.72		

This table shows non statistically significant deference between three groups regarding BMI when p-value was >0.05.

2-As regard to type of surgery:

Table (5): Type of surgery.

	Groups							
	Dexmedetomedine		Propofol		Midazolam		Chi-square	
	N	%	N	%	N	%	X2	P-value
Total colectomy	17	56.7	15	50.0	16	53.3	0.268	0.875
Partial gastrectomy	8	26.7	10	33.3	11	36.7	0.712	0.700
Radical cystectomy	3	10.0	3	10.0	2	6.7	0.274	0.872
Whipple's operation	2	6.7	2	6.7	1	3.3	0.424	0.809

3- As regard to haemodynamic changes:

a- The MAP readings show highly statistically significant difference between the three groups regarding MAP (mmHg) when p-value was <0.001** at 6 hrs. to 48 hrs (table 6).

Table (6): Comparison between three groups regarding MAP (mmhg)

MAP	Dexmedetomedine		Propofol		Midazolam		Tukey's test		
(mmHg)	Mean	SD	Mean	SD	Mean	SD	P1&P2	P1&P3	P2&P3
0 hrs.	103.20	4.99	104.57	4.92	105.73	5.28	0.879	0.473	0.228
6 hrs.	96.20	4.51	92.00	3.70	99.13	5.06	<0.001**	0.033*	<0.001**
12 hrs.	94.57	4.75	88.00	3.84	97.27	4.78	<0.001**	0.056	<0.001**
18 hrs.	92.20	4.95	87.00	4.09	96.37	5.10	<0.001**	0.003*	<0.001**
24 hrs.	95.00	4.96	85.20	4.09	95.77	5.09	<0.001**	0.806	<0.001**
30 hrs.	90.20	4.66	86.27	4.28	97.43	4.79	0.004*	<0.001**	<0.001**
36 hrs.	92.07	5.08	86.27	4.28	99.02	4.87	<0.001**	<0.001**	<0.001**
42 hrs.	91.60	5.30	87.03	4.73	99.97	4.87	0.002*	<0.001**	<0.001**
48 hrs.	91.93	5.02	86.43	4.19	100.97	4.16	<0.001**	<0.001**	<0.001**

This table shows a highly statistical significant deference between group P with group D and group M regarding MAP (mmHg) when p-value was <0.001** at 6 hrs. to 48 hrs.

b. The heart rate readings show highly statistical significant difference between group D with group P and group M regarding HR (bpm) when p-value was <0.001** at 6 hrs. to 48 hrs (table 7).

Table (7): Comparison between three groups regarding HR.

HR	Dexmedetomedine		Propofol		Midazolam		Tukey's test		
(BPM)	Mean	SD	Mean	SD	Mean	SD	P1&P2	P1&P3	P2&P3
0	97.24	5.94	94.50	6.46	96.27	5.46	0.188	0.806	0.489
6	84.60	5.72	89.23	6.49	93.37	5.68	0.010*	<0.001**	0.024*
12	75.60	6.33	86.43	6.55	87.73	22.19	0.009*	0.003*	0.930
18	73.20	5.90	86.17	6.67	87.00	22.00	<0.001**	<0.001**	0.970
24	72.93	5.79	85.97	6.83	86.97	21.95	<0.001**	<0.001**	0.957
30	72.87	5.54	85.73	6.32	91.53	5.67	<0.001**	<0.001**	<0.001**
36	72.63	6.23	85.97	6.60	91.73	5.62	<0.001**	<0.001**	<0.001**
42	72.90	5.86	85.70	6.34	91.83	5.49	<0.001**	<0.001**	<0.001**
48	72.33	5.92	85.73	6.53	91.67	5.57	<0.001**	<0.001**	<0.001**

3- As regard to SO2 readings show statistical significant difference between group D and group P regarding SpO2 (%) when p-value was <0.05* at 6 hrs. to 24 hrs. and statistical significant difference between group D with and group M at 24 hrs. while non statistical significant difference between three groups in others times when p-value was >0.05 (table 8).

Table (8): Comparison between the three groups regarding SpO2 (%).

SpO2 (%)	Dexmedetomedine		Propofol		Midazolam		Tukey's test		
	Mean	SD	Mean	SD	Mean	SD	P1&P2	P1&P3	P2&P3
0	98.03	0.85	98.13	1.01	97.93	0.94	0.910	0.910	0.687
6	97.37	0.76	96.83	0.87	97.00	0.87	0.041*	0.213	0.722
12	97.17	0.87	96.57	0.97	96.87	0.97	0.041*	0.436	0.436
18	97.27	0.91	96.40	1.00	96.70	0.99	0.002*	0.066	0.456
24	97.40	0.72	96.60	1.04	96.80	0.96	0.003*	0.035*	0.677
30	97.20	0.73	96.83	0.82	96.85	0.90	0.070	0.103	0.928
36	97.17	0.90	96.77	0.85	96.87	0.94	0.082	0.211	0.667
42	97.03	0.77	96.60	0.93	96.90	0.96	0.061	0.565	0.223
48	96.77	0.82	96.47	0.83	96.93	0.98	0.140	0.495	0.058

4- As regard to RASS, readings show highly statistically significant difference between group D with group P and group M regarding RASS when p-value was <0.001** at 6 hrs. to 24 hrs. while, non-statistical significant difference between group P and group M when p-value was >0.05 (table 9).

Table (9): Comparison between the three groups regarding RASS.

RASS	Dexmedetomedine		Propofol		Midazolam		Tukey's test		
	Mean	SD	Mean	SD	Mean	SD	P1&P2	P1&P3	P2&P3
0	3.03	0.18	3.00	0.01	3.00	0.01	0.442	0.442	1.000
6	-0.80	0.55	-1.33	0.48	-1.53	0.57	<0.001**	<0.001**	0.322
12	-1.03	0.61	-1.73	0.64	-1.53	0.51	<0.001**	0.004*	0.392
18	-1.03	0.61	-1.73	0.64	-1.53	0.51	<0.001**	0.004*	0.392
24	-1.07	0.64	-1.73	0.64	-1.53	0.51	<0.001**	0.009*	0.403
30	-1.23	0.71	-1.43	0.74	-1.53	0.51	0.289	0.065	0.544
36	-1.43	0.61	-1.53	0.75	-1.57	0.57	0.573	0.362	0.816
42	-1.25	0.55	-1.42	0.50	-1.50	0.57	0.110	0.089	0.565
48	0.07	0.25	0.00	0.00	0.00	0.00	1.000	1.000	1.000

5- As regard to CPOT show highly statistically significant difference between three group regarding CPOT when p-value was <0.001** at 6 hrs. to 24 hrs. while non statistically significant difference between three group when p-value was >0.05 (table 10).

Table (10): Comparison between three groups regarding CPOT.

CPOT	Dexmedetomedine		Propofol		Midazolam		Tukey's test		
	Mean	SD	Mean	SD	Mean	SD	P1&P2	P1&P3	P2&P3
0 hrs.	6.17	1.02	6.00	1.05	5.70	1.06	0.810	0.198	0.507
6 hrs.	2.97	0.85	5.73	0.91	4.97	0.85	<0.001**	<0.001**	0.003*
12 hrs.	1.70	0.88	4.83	0.79	3.60	0.56	<0.001**	<0.001**	<0.001**
18 hrs.	3.07	0.98	4.20	0.81	3.73	0.64	<0.001**	0.006*	0.076
24 hrs.	1.87	0.82	4.10	0.76	3.43	0.57	<0.001**	<0.001**	0.002*
30 hrs.	3.63	1.46	4.10	0.86	4.02	0.56	0.134	0.177	0.671
36 hrs.	3.77	1.19	4.20	0.81	4.05	0.56	0.107	0.248	0.407
42 hrs.	2.83	0.50	3.13	0.87	3.17	0.89	0.106	0.073	0.860
48 hrs.	2.13	0.43	2.47	1.10	2.30	0.51	0.120	0.168	0.445

6- As regard to analgaesic requirements (nalbuphine requirement) show highly statistically significant deference between three groups regarding nalbuphine_mg when p-value was <0.001** (table 11).

Table (11): Nalbuphine requirement.

Groups	Nalbuphine_(mg)						ANOVA	
	Range			Mean	±	SD	f	P-value
Dexmedetomedine	0	-	40	19.67	±	14.02	35.365	<0.001**
Propofol	0	-	130	73.33	±	32.31		
Midazolam	0	-	120	58.17	±	26.60		
Tukey's test								
Group I & Group II				Group I & Group III			Group II & Group III	
<0.001**				<0.001**			0.060	

7- As regard to time to extubation readings show highly statistical significant difference between three groups regarding time to extubation (hr) when p-value was < 0.001** (table 12).

Table (12): Comparison between the three groups regarding admission to extubation time (hr).

Groups	Admission to extubation time(hrs)						ANOVA	
	Range			Mean	±	SD	f	P-value
Dexmedetomedine	24	-	31	28.33	±	2.20	430.115	<0.001**
Propofol	40	-	51	46.90	±	3.19		
Midazolam	38	-	45	41.73	±	2.05		
Tukey's test								
Group I & Group II				Group I & Group III			Group II & Group III	
<0.001**				<0.001**			<0.001**	

8- As regard to extubation time showed significant difference between the three groups regarding extubation time when p-value < 0.001 (table 13).

Table (13): Comparison between the three groups regarding drug discontinuation to extubation.

Groups	Drug discontinuation to extubation time(min.)						ANOVA	
	Range			Mean	±	SD	f	P-value
Dexmedetomedine	55	-	66	60.73	±	3.33	919.359	<0.001**
Propofol	65	-	76	71.20	±	3.12		
Midazolam	95	-	110	101.40	±	4.77		
Tukey's test								
Group I & Group II				Group I & Group III			Group II & Group III	
<0.001**				<0.001**			<0.001**	

9- As regard to length of ICU stay (LOS) readings This table show highly statistically significant difference between three groups regarding ICU_LOS(h) when p-value was <0.001** (table 14).

Table (14): Comparison between the three groups regarding length of ICU stay (hrs).

Groups	length of ICU stay(hrs)						ANOVA	
	Range			Mean	±	SD	f	P-value
Dexmedetomedine	55	-	66	60.43	±	3.17	499.701	<0.001**
Propofol	70	-	83	76.67	±	3.46		
Midazolam	80	-	91	86.33	±	2.97		
Tukey's test								
Group I & Group II				Group I & Group III			Group II & Group III	
<0.001**				<0.001**			<0.001**	

DISCUSSION

The process of weaning from mechanical ventilation is central to the management of critically ill patients. It is a very complex and difficult task. Attention should be paid to wean off the ventilator as quickly as possible after the conditions that warranted placing the patient on the ventilator begin to resolve and stabilize [5].

Delayed or unnecessarily prolonged weaning increases length of intensive care unit (ICU) stay, health-care cost, decreases the ICU bed availability and adversely affects patient outcome. Aggressiveness in weaning off the ventilator, however, must be balanced against the possibility that premature discontinuation may occur. Premature discontinuation carries its own set of problems, including difficulty in reestablishing artificial airways and compromised gas exchange, etc [6].

Majority of ICU patients who are on ventilatory support require intravenous (i.v.) sedative and analgesic medications to facilitate mechanical ventilation, improve tolerance to the endotracheal tube, the invasive procedures, physiotherapy, tracheal suctioning, turning postures, changing of dressings, allays anxiety, blunts excessive hemodynamic, and metabolic responses [11].

The ideal drug for sedation in the ICU is one with a rapid onset of action, a short duration of action and which produces sedation without affecting the cardiovascular or respiratory system. It should have a short elimination half-life with no accumulation on repeated or continuous administration, and should be metabolized by pathway not dependent on renal, hepatic, or pulmonary functions. Etomidate, opioids, benzo-diazepines, thiopentone, and ketamine are few examples which individually lacked some of these desirable properties and hence failed to become the drug of choice [12].

The α2 agonist dexmedetomidine is a newer sedative and analgesic agent used for ICU sedation for up to 24 h after surgery. It provides a hemodynamic stability and appears to have no clinically important adverse effects on respiration. Its sedative properties are unique in that it produces only mild cognitive impairment, allowing easy communication between health-care provider and patient in the ICU. It does not affect the respiratory drive and therefore, it should not interfere with weaning from mechanical ventilation [13].

Dexmedetomidine is a new, potent alpha-2 agonist acting in the locus ceruleus, inhibits sympathetic stimulation, and provides analgesia and sedation without respiratory depression and hemodynamic instability. It

produces only mild cognitive impairment allowing easy communication between health-care provider and the patient in ICU [13].

Haemodynamic parameters:

As regard to HR

In this study there was a significant reduction in the heart rate of the Dexmedetomidine group compared to the Propofol group and midazolam group, with p-value (<0.001), this coincides with study performed by Samson et al. (14) who found that patients receiving dexmedetomidine have significantly lower HR compared to propofol and midazolam, during sedation mean pulse rate in dexmedetomidine group was 77.54 ± 9.34, in propofol group 89.34 ± 10.1 and for midazolam group 90.23 ± 10.7.

This also coincides with the study performed by ***Jacob and co-workers*** [15], which stated that as an alpha2-adrenoreceptor agonist, dexmedetomidine can cause bradycardia and hypotension.

Also, this accord with that found by ***Gupta and coworkers*** [16] who showed that the heart rate in the dexmedetomidine group was significantly lower than that in the midazolam group at 16, 20, and 24 h after the drug infusion. In the intragroup comparison, the mean fall in heart rate from the baseline values was significant in dexmedetomidine group at 16, 20, and 24 h, whereas, it was insignificant in midazolam group.

Also, agree with study performed by ***Srivastava and colleagues*** [17] in comparison of dexmedetomidine, propofol and midazolam for short-Term sedation in postoperatively mechanically ventilated neurosurgical patients . They stated that the hypotension and bradycardia that occurred in the dexmedetomidine group were predictable from the known properties of α2 agonists.

As in previous studies, bradycardia was more common with Dexmedetomidine [18]. Also this coincides with the study performed by ***Ruokonen and his co-workers*** [19] and confirm results received by ***Riker and his co-workers*** [20].

As regard to MAP

In this study there was a reduction in MAP in dexmedetomedine group and propofol groups in comparison with midazolam group.This conclusion is similar to that found by ***Srivastava and coworkers*** [17] who indicated that dexmedetomidine is known to decrease sympathetic outflow and circulating catecholamine levels and would therefore be expected to cause a decrease of MAP similar to those of propofol. The hypotension and bradycardia that occurred in the dexmedetomidine group were predictable from the known properties of α2 agonists.

This study results are similar to that found by ***Samson et al.*** [14] who stated that there was fan in blood pressure measurement in all the three studied groups (dexmedetomedine, propofol and midazolam).

The present conclusion also coincides with that found by ***Gupta and co workers*** [16] on the role of dexmedetomedine in early extubation in icu and showed that there was a significant fall of MAP from baseline which was observed at 20 h and 24 h in dexmedetomidine group compared to midazolam group.

In the MIDEX trial, the adverse event hypotension was recorded in 29 of 250 midazolam patients (11.6%) vs 51 of 247 dexmedetomidine patients (20.6%) (P=.007). Bradycardia was reported in13 of 250 midazolam patients (5.2%) and in 35 of 247 dexmedetomidine patients (14.2%) (P_.001). In the PRODEX trial, hypotension and bradycardia were reported at similar rates in both propofol and dexmedetomedine groups [15].

Changes in CPOT and analgaesic requirment

In this study there were significant differences (p-value for the CPOT score <0.001 from the start of sedation till 24 hours, and p-value for the nalbuphin consumption<0.001) between the three groups as regards the pain score and total analgesic requirements, like the study performed by ***ELbaradie and colleagues*** [21] in their randomized clinical study conducted to compare dexmedetomidine vs. propofol for short-term sedation of postoperative mechanically ventilated patients They found that patients receiving propofol infusions required significantly more fentanyl (75±15 mcg) compared to patients receiving dexmedetomidine (15±10.5 mcg), with p value = 0.005.

Our results are in agreement with those found by ***Srivastava and coworkers*** [17] who did a comparison between dexmedetomedine, propofol and midazolam in postoperative neurosurgical patients and stated that an equivalent depth of sedation between dexmedetomidine, propofol and midazolam was achieved, with the advantage that the total amount of fentanyl required by the dexmedetomidine group was less.

Also agrees with the study performed by ***Ruokonen et al.*** [19] who compared between dexmedetomidine and propofol for sedation in the ICU and stated that the opioids requirements were reduced by 50% in the patients who received dexmedetomidine.

The interaction of α2-adrenoreceptors and opioids lead to decrease in the dose of fentanyl. The α2 adrenoceptors have an effect on the spinal cord, especially α2 A and α2 C as well as modulating the descending noradrenergic pathways leading to 30% to 50% reduction in the requirements of opioids. Our study is in accordance with other studies [20].

Changes in the RASS scale:

In this study there were significant differences (p-value <0.001 from 6hours from starting sedative time to 24 hours) in the RASS score between the groups although both drugs produced the desired degree of sedation, with better communication and arousability for the patients receiving dexmedetomidine.

Two randomized control trials were performed by ***Jacob and his co-workers*** [15], to determine the efficacy of dexmedetomidine vs midazolam or propofol in maintaining sedation; reducing duration of mechanical ventilation; and improving patients' interaction with nursing care . They found that dexmedetomidine patients had higher actual RASS scores in both studies.

Time to extubation

In this study there were significant differences (p-value <0.001) in the time to extubation between dexmedetomidine compared to propofol and midazolam with faster time for dexmedetomidine receiving patients (28 hours for most of the patients in the dexmedetomidine group vs 46 hours for most of the patients in the propofol group and 41 hours for most of the patient in the midazolam group)., this comes with the results performed by ***Gupta and co-workers*** [16] which stated that the time to extubation in the dexmedetomidine group (24.210 ± 1.6651 h) was found to be significantly lower (7.14 h) than in the midazolam group (31.350 ± 3.3447 h) and with that was done by ***Shehabi et al.*** [21] in 2004 and showed that the mean time to extubation was shorter in dexmedetomidine group (24.21 h [22-28 h]) than midazolam group (31.35 h [26-38 h] [P < 0.05]).

Similar to this study, work was done by ***Arpino and colleagues*** [22], to assess feasibility of dexmedetomidine in facilitating extubation in the intensive care unit. They demonstrated that all of their patients had proven difficult to wean and extubate.

This study differs from the study performed by ***Daniel L. Herr and colleagues*** [23], who compared ICU Dexmedetomidine-based and propofol-based sedation regimens after coronary artery bypass graft surgery and displayed that there were no differences in times to weaning or extubation between dexmedetomidine and propofol, mostly this was because propofol was actually administered for only a part of each patient's time in the ICU, not all the period of ICU stay, so the patients were easily arousal and better communicating whereas dexmedetomidine was administered continuously from entry to exit.

The present study differs from that performed by ***Jakob and colleagues*** [18] who underwent 2 randomized control trials to compare dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation. .They indicated that the median length of stay in the ICU from randomization until the patients were medically fit for discharge was not significantly different in the 2 studies (midazolam 243 hours vs dexmedetomidine 211 hours and propofol 185 hours vs dexmedetomidine 164hours) [15]. And this may be because of the long length of the patients' ICU stay and this was confirmed by Zhi-Qui xia and colleagues in their meta-analysis of randomized control trials which suggested that when it came to patients with longer lengths of ICU stay, the beneficial effect of dexmedetomidine in reducing the length of ICU stay did not exist, possibly because more opioids and other medications were used and ventilator-related diseases developed during the ICU stay that complicated the situation [24].

CONCLUSION

From this study we concluded that dexmedetomidine has clinically relevant benefits compared to midazolam and propofol in facilitating extubation because of its shorter time to extubation, more hemodynamic stability, easy arousability and lack of respiratory depression; hence, it can be used as an effective, and safe sedative agent to facilitate extubation in ICUs and decreasing ICU length of stay.

REFERENCES

1. **Barr J, Fraser GL, Puntillo K *et al.* (2013):** Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med., 41:263–306.
2. **Hughes CG, McGrane S and Pandharipande PP (2012):** Sedation in the intensive care setting. Clin Pharmacol., 4:53-63.
3. **Devlin JW and Roberts RJ (2011):** Pharmacology of commonly used analgesics and sedatives in the ICU: benzodiazepines, propofol, and opioids. Anesthesiol Clin., 29(4):567-85.
4. **Jackson DL, Proudfoot CW, Cann KF *et al.* (2010):** A systematic review of the impact of sedation practice in the ICU on resource use, costs and patient safety. Crit Care, 14:R5.

5. **MacIntyre NR, Cook DJ, Ely EW Jr, Epstein SK, Fink JB, Heffner JE *et al.* (2001):** Evidence-based guidelines for weaning and discontinuing ventilatory support: A collective task force facilitated by the American College of Chest Physicians, the American Association for Respiratory Care, and the American College of Critical Care Medicine. Chest, 120:375S-95.
6. **Kress JP, Pohlman AS, O'Connor MF *et al.* (2000):** Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med., 342:1471-7.
7. **Hsu YW, Cortinez LI, Robertson KM *et al.* (2004):** Dexmedetomidine pharmacodynamics. Part I: Crossover comparison of the respiratory effects of dexmedetomidine and remifentanil in healthy volunteers. Anesthesiology, 101:1066–76.
8. **Sessler CN and Varney K (2008):** Patient-focused sedation and analgesia in the ICU. Chest, 133(2):552-565.
9. **Ely EW, Truman B, Shintani A *et al.* (2003):** Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA., 289(22):2983–2991.
10. **Gélinas C, Fillion L, Puntillo KA, Viens C and Fortier M (2006):** Validation of the critical-care pain observation tool in adult patients. American Journal of Critical Care, 15(4):420-7.
11. **Arroliga A, Frutos-Vivar F, Hall J et al. (2005):** Use of sedatives and neuromuscular blockers in a cohort of patients receiving mechanical ventilation. Chest, 128:496-506.
12. **Botha J and Le Blanc V (2005):** The state of sedation in the nation: Results of an Australian survey. Crit Care Resusc.,7:92-6.
13. **Sudheesh K and Harsoor SS (2011):** Dexmedetomidine in anaesthesia practice: A wonder drug?. Indian J Anaesth ., 55:323-4.
14. **Samson S, George SK, Vinoth B, Khan MS and Akila B (2014):** Comparison of dexmedetomidine, midazolam, and propofol as an optimal sedative for upper gastrointestinal endoscopy: A randomized controlled trial. Journal of Digestive Endoscopy, 5(2):51.
15. **Jacob S, EskoRuokonen, R, Grounds M, Sarapohja T (2012):** Dexmedetomidine vs Midazolam or Propofol for Sedation During Prolonged Mechanical Ventilation Two Randomized Controlled Trials. JAMA., 307(11):1151-1160.
16. **Gupta S, Singh D, Sood D, Kathuria S (2015):** Role of dexmedetomidine in early extubation of the intensive care unit patients. Journal of Anaesthesiology Clinical Pharmacology, 31 (1):92-97.
17. **Srivastava VK, Agrawal S, Kumar S, Mishra A, Sharma S, Kumar R (2014):** Comparison of dexmedetomidine, propofol and midazolam for short-term sedation in postoperatively mechanically ventilated neurosurgical patients. Journal of clinical and diagnostic research: JCDR., 8(9):GC04.
18. **Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, Bratty JR, Takala J (2012):** Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA., 307(11):1151-60.
19. **Ruokonen E, Parviainen I, Jakob SM, Nunes S, Kaukonen M, Shepherd ST, Sarapohja T, Bratty JR and Takala J (2009):** Dexmedetomidine versus propofol/ midazolam for long-term sedation during mechanical ventilation. Intensive care medicine, 35(2):282-90.
20. **Bajwa SJ, Kaur J, Singh A et al. (2012):** Attenuation of pressor response and dose sparing of opioids and anaesthetics with pre-operative dexmedetomidine. Indian J Anaesth., 56(2):123-28.
21. **Elbaradie S, El-Mahalawy F H, and Soliman AH (2015):** Dexmedetomidine vs. Propofol for Short-Term Sedation of Postoperative Mechanically Ventilated Patients. 2004, Journal of the Egyptian Nat. Cancer Inst., 16(3):153-8.
22. **Arpino D P, Kalafatas K and Thompson B (2008):** Feasibility of dexmedetomidine in facilitating extubation in the intensive care unit. Journal of Clinical Pharmacy and Therapeutics, 33: 25-30.
23. **Herr DL, John Sum-Ping, and England M (2003):** ICU Sedation After Coronary Artery Bypass Graft Surgery: Dexmedetomidine-Based Versus Propofol-Based Sedation Regimens. Journal of Cardiothoracic and Vascular Anesthesia, 17(5): 576-584.
24. **Zhi-Qiu Xia, Shu-Qin Chen, Xi Yao *et al.* (2013):** Clinical benefits of dexmedetomidine versus propofol in adult intensive care unit patients: a meta-analysis of randomized clinical trials. Journal of surgical research, 25:22-36.