Comparative Study between Dexmedetomidine and Propofol as Sedatives after Cardiac Surgery

Ahmed Mohamed Shawky[1], Ahmed Mohamed Abd-Alrahman Tahoun[2], Ahmed Said Abd-Alrahman[1], Usama Ibrahim Abd-Alkarim[1], Ahmed Mosaad Ahmed El-Naggar[1]

[1]Department of Anesthesiology and Intensive Care, Faculty of Medicine, Al-Azhar University, Egypt
[2] Department of clinical pathology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
ett883@yahoo.com

Abstract: **Background:** Sedation in mechanically ventilated cardiac patients presents a unique therapeutic dilemma in which the provider must balance patient comfort with the potentially negative consequences of drug exposure**. The aim of this study** was to compare dexmedetomidine topropofol in the provision of sedation and analgesia, time to extubation, their effects on hemodynamic and respiratory parameters and early post-operative complication after cardiac surgery and Investigators overall assessment of the sedative agent. **Materials and Methods:** A prospective, randomized single-blinded trial was conducted on 60 cardiac surgery patients in the ICU. Patients were assigned into equal propofol and dexmedetomidine groups. At start of skin closure, with no loading dose Infusion rate was at 3mg /kg /h in the range of 1-6 mg/kg/h for propofol and 0.4 µg/kg/h in the range of 0.2-0.7 µg/kg/h for dexmedetomidine and for both groups morphine was the only rescue analgesic. Riker sedation-agitation scale and Critical care pain observation tool were used. **Results:** Patients sedated with dexmedetomidine required significantly lower dose of morphine compared to propofol [total morphine 4.19 mg ± 0.96 and 9.15 ± 2.19 respectively, p <0.001*]. Mean heart rate and mean blood pressure, time to wean and time to extubation were also significantly lower in dexmedetomidine group compared to propofol group. Incidence of shivering in dexmedetomidine was significantly lower than propofol 33.3% and 7.1% p=0.015*. However There was no significant difference between groups as regard percentage of time spent at (SAS4) in relation to the total sedation time, it was 54.12 % ± 18.61 for propofol and 47.12 % ± 16.37, p=0.144. Also there were no significant differences in the other parameters between the two groups. **Discussion and Conclusions**: Dexmedetomidine is comparable to propofol in the provision of sedation, and its effect on hemodynamics and respiratory parameters. However it has added advantages in the provision of analgesia, and a significant reduction in heart rate and decrease time to wean and time to extubate without causing significant complication.

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1. Introduction

Recent guidelines of sedation reported that analgesics and sedatives must be carefully titrated to the individual needs, as deep sedation prolongs weaning from mechanical ventilation and potentially increases morbidity. On the other hand, inadequate sedation can result in anxiety, agitation and recall of stressful experience in the post-operative ICU phase [3]. Strategies using non benzodiazepine sedatives either propofol or dexmedetomidine may improve clinical outcomes in mechanically ventilated adult ICU patients [10]. The current standard for sedation in post-operative cardiac surgery patients are propofol. It has a rapid onset and a very short duration of action. However it has been associated with dose-dependent respiratory depression, hypotension and hyperlipidemia. Hence, it can exert deteriorating effects in patients with limited myocardial reserve. Consequently, clinicians have adapted its use to minimize these risks and avoid respiratory depression by discontinuing it before extubation butthis effectively eliminates the calming effects of sedation at times of high stress [15].

In 1999, the Food and Drug Administration (FDA) approved the use of dexmedetomidine as an alternative to GABA-mimetic drugs for ICU sedation [46]. It is α2-adrenoceptor agonist, which has been shown to provide sedation and analgesia with minimal respiratory depression. This occurs via central nervous system receptors, particularly in the locus coeruleus, regulating memory, awareness, and nociception [6]. It has analgesic properties and one could reasonably expect that the use of narcotics would be lower. If patients had less pain and received fewer narcotics, early recovery would be feasible and patients might be fast-tracked extubation within6 hour post-operative.

In this trial the authors assumes that routine use of dexmedetomidine after cardiac surgery would be

superior to propofol in time to extubation, analgesic use, also continuing dexmedetomidine during extubation decrease stress and facilitate it without major adverse effect on the patients' vital status.

Primary outcome of the study was the percentage of timeat which patients was calm and co-operative (SAS 4) in relation to the whole sedation time.

Secondary outcomes were Time to achieve (SAS 4), time to weaning, time to extubation, postoperative analgesic needs, early postoperative hemodynamic, respiratory status, also early post-operative complication and Investigators overall assessment of the sedative agent.

2. Materials and Methods:

After Research / Ethics committee approval of the faculty of medicine, Al Azhar University at Al-Hussain university hospital and obtaining written informed consent the trial was conducted on 60 cardiac surgery patients in the ICU. Riker sedation-agitation scale (tab. 1) and Critical care pain observation tool (tab. 2) were used for sedation and pain management in this trial.

Tab. 1: Riker Sedation-Agitation Scale (SAS) ***(Riker et al., 1999) [52]***

Score	Definition	Description
7	**Dangerous Agitation**	Pulling at endotracheal tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side
6	**Very Agitated**	Requiring restraint and frequent verbal reminding of limits, biting endotracheal tube
5	**Agitated**	Anxious or physically agitated, calms to verbal instruction
4	**Calm and Cooperative**	Calm, easily arousable, follows commands
3	**Sedated**	Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
2	**Very Sedated**	Arouses to physical stimuli but does not communicate or follow commands, may move sponta-neously
1	**Unarousable**	Minimal or no response to noxious stimuli, or follow commands

Tab. 2: Critical Care Pain Observation Tool (CPOT scale) (*Gélinas et al., 2009) [53]*

Indicator	Score		Description
Facial expression	Relaxed, neutral	**0**	No muscle tension observed
	Tense	**1**	Presence of frowning, brow lowering, orbit tightening and levator contraction or any other change (e.g. opening eyes or tearing during nociceptive procedures)
	Grimacing	**2**	All previous facial movements plus eyelid tightly closed (the patient may present with mouth open or biting the endotracheal tube)
Body movements	Absence of movements or normal position	**0**	Does not move at all (doesn't necessarily mean absence of pain) or normal position (movements not aimed toward the pain site or not made for the purpose of protection)
	Protection	**1**	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements
	Restlessness/Agitation	**2**	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed
Compliance with the ventilator (intubated patients)	Tolerating ventilator or movement	**0**	Alarms not activated, easy ventilation
	Coughing but tolerating	**1**	Coughing, alarms may be activated but stop spontaneously
	Fighting ventilator	**2**	Asynchrony: blocking ventilation, alarms frequently activated
Or **Vocalization (extubated patients)**	Talking in normal tone or no sound	**0**	Talking in normal tone or no sound
	Sighing, moaning	**1**	Sighing, moaning
	Crying out, sobbing	**2**	Crying out, sobbing
Muscle tension Evaluation by passive flexion and extension of upper limbs when patient is at rest or evaluation when patient is being turned	Relaxed	**0**	No resistance to passive movements
	Tense, rigid	**1**	Resistance to passive movements
	Very tense or rigid	**2**	Strong resistance to passive movements or incapacity to complete them
Total	0-8		

Inclusion criteria;

- **Age:** adult patients (18 - 60) years.
- **Sex:** both sexes.
- **ASA physical status:** II, III
- **Operation:** elective cardiac surgeries Defined as (isolated coronary revascularization and or

single-valve repair/replacement surgery or multiple valves repair/replacement).

Exclusion criteria;

Poor cardiac function (Left ventricular ejection fraction of less than 40%, infective endocarditis still on antibiotic medication, Congestive heart failure, cardiogenic shock and myocardial infarction within the previous 6 weeks). Pre-existing profound bradycardia (heart rate ≤ 55) or Second or third degree heart block required pacemaker or atrial fibrillation. Surgery requiring deep hypothermic circulatory arrest or involving the thoracic aorta or off-pump coronary artery bypasses surgery and previous cardiac surgery (a redo-sternotomy).

Severe chronic obstructive pulmonary disease (long-term use of bronchodilators or steroids for lung disease and stage 3 of GOLD Staging System for COPD Severity (FEV1/FVC ratio less than 70 percent and FEV1 30%- 50% less than predicted value, Obese patients (BMI > 30) or history of obstructive sleep apnea, Chronic Renal insufficiency (creatinine >2mg/dl), Chronic liver disease (more than stage A modified child-Pugh score), Pituitary, adrenal or thyroid disorders and pregnant or lactating females, Uncontrolled diabetes mellitus (Hemoglobin A1c >7%), central nervous system problems (seizure, previous stroke, delirium, severe dementia and psychiatric disorder) and Recent use (one month before surgery) of Drugs that might influence outcome (narcotics, Psychotropic medications, dexmedetomidine. or other α2-agonists or antagonist or Chronic alcohol abusers and allergy to any of the study medications.

Major intraoperative insults that were expected to prolong postoperative mechanical ventilation time beyond (first 6 hours after surgery) as; Cardiopulmonary Bypass time (CPBT) more than 180 min, aortic cross clamp time (AXCT) more than 90 min. Difficult to wean from CPB due to Structural abnormalities, Dynamic abnormalities, Ventricular systolic dysfunction and Vasoplegic syndrome, Patients with heart block needed pacing to control HR, Patient needed mechanical circulatory support and Patients were on high level of inotropic support at the end of subcutaneous hemostasis after closure of sternotomy (**defined as** use of two or more of the following: Dobutamine >10 µg/kg/min, Dopamine >10µg/kg/min, Epinephrine >0.2µg/kg/min, Milrinone >0.75µg/kg/min).

Randomization

Patients were randomly allocated into one of two equal groups, either dexmedetomidine or propofol group (control) according to a computer generated randomization code using random allocation software® program, version 1.0.0. It was consist of 10 randomized blocks each had 6 numbers divided equally between the two groups aiming at subject allocation in a 1:1 ratio. Opaque sealed envelopes was opened at the end of sternal closure and before staring of skin closure (time needed for preparation of the sedative drug).

End point of the study

It was 6 hour post ICU admission or 1 hour post extubation which was later and Patients had been excluded from the study and shifted to other sedation protocol that was individually determined If any of the following occurred after Study Drug Administration; if patient not extubated within time end point, if there was Violation of the study protocol, Patients needed surgical re-exploration, if sedative infusion was stopped for management of a complication developed postoperatively.

If significant adverse eventoccurred that was expected to abandonment of patients from fast track-extubation as; **Cardiovascular adverse event,** Significant hypotension (MAP less than 60 mm Hg or systolic pressure less than 80 mm Hg) In spite of optimization of preload, heart rate, metabolic state. If electrical cardioversion or high level of inotropic, vasopressor was needed. Profound bradycardia need treatment was defined as (heart rate <55). **Respiratory adverse event as**; persistent hypoxemia (spo 2< 94% for more than I hour) in spite of full ventilatory supports (Assisted/Control ventilatory mode with high fio 2%) was done. **Delayed neurological recovery**; "patient still deeply sedated (< SAS 3) by the end of the 3rd hour ICU admission, despite minimum rate of sedative infusion. **Sever metabolic disturbance**; persistent disturbance (pH ≥7.50 or ≤7.20 for more than 1 hour after surgery) in spite of proper management of the causes or persistent shivering requiring meperidine management.

Anesthesia and CBP were standardized in both groups. Intraoperative fentanyl and midazolam was limited to the pre bypass period and to a maximum 10 µg/kg and 0.1 mg/kg respectively and. No muscle relaxant was given after weaning from CPB. Immediately before start of sternal closure 1.5 µg/kg fentanyl bolus was given for all patients. *Total intraoperative Fentanyl and propofol, Total bypass time and aortic cross clamping time were recorded.*

At start of skin closure, intra operative inhalational anesthetic wasdiscontinued and study drug was started.

Weaning and extubation protocol were standardized in both groups. Patient was considered ready to **start weaning** and *Time to wean was recorded*when; demonstrates signs of awakening from anesthesia ≥ SAS 2, Core temp ≥ 36^0c, Patient has gross spontaneous muscle movement, Haemodynamically stable; HR and BP were within ordered parameters (HR 60-120 and MAP >65), No

acute ischemia, Absence of new arrhythmia, Blood loss < 2cc/kg/ hour, Urine output > 1cc/kg/hour, Spo2 ≥ 92 on FiO_2 ≤50 %, Chest x ray film (mediastinum without widening, adequate expansion of both lungs, absence of major pleural fluid, absence of pneumothorax, absence of infiltrates and minimal pulmonary vascular congestion).

Extubation was done and *Time to extubation was recorded* if the following conditionswere fulfilled; Patient was awake, or arousable SAS ≥ 3, move all extremities on command, able to lift head off pillow, nods appropriately to questions and intact Cough reflex. Temp was ≥ 37^0c, haemodynamically stable; HR and BP were within accepted parameters (HR 60-120 and MAP >65) with no need for inotropic support or vasopressor except for dopamine <5 µg/kg/min), No acute ischemia and Absence of new arrhythmia. Blood loss was < 1cc/kg/h and Urine output >1cc/kg/h. Adequate oxygenation (O2 saturation > 94%, P/F ratio > 200, Spontaneous tidal volumes > 5 cc/kg, RR <30 bpm, Negative inspiratory force (NIF) < -20 cmH_2O and minute ventilation Minute ventilation V_E ≤ 10 lpm on fio2 < 0.4 %, positive end expiratory pressure (PEEP) ≤ 8 cmH2o and pressure support (PS) ≤ 10 cmH2O and if Rapid shallow breathing index (RSBI) (Tobin index) was F/Vt < 80. Accepted ABG pH; 7.35 - 7.50 (base excess ≤ 4), PCO2 < 45 or patients normal value if Co2 retainer, PaO2 ≥ 80 with fio2<40.

Statistical Analysis:

- Data were collected, coded, tabulated, and then analyzed using SPSS statistical software package (V. 15.2, Echo soft Corp., USA, 2006).
- The data were given as (the mean, standard deviation) or (median, interquartile range) or (numbers and percent) where appropriate.
- Comparison between the two groups for numerical data was performed with independent sample *t*-test if they showed normal distribution, otherwise Mann- Whitney test was used as in ordinal data (CPOT and SAS).
- Nominal variables were compared by chi-square test or fisher exact test.
- Within-group comparisons were done by the paired samples *t*-test.
- The P value<0.05 was considered statistically significant.

3. Results

A total of (5) patients were excluded from this trial after randomization, 2 patients was excluded due to violation of the study protocol, one patient due to delayedrecovery after surgery, one patient developed complete heart block that needed pacemaker after aortic valve replacement surgery the last one was excluded due to surgical reexploration after CABG surgery. A Total 27, 28 patients in propofol and dexmedetomidine groups respectively continued the study and their data were statistically analyzed.

The two groups were similar in patients' characteristics (*P* >0.05) (Tab. 1). Results demonstrated also no significant differences as regard surgery, anesthesia-related variables between groups (Tab. 2, 3).

Tab. 1: Patient Characteristics

Variable		propofol		dexmedetomidine		p value
gender	male	13	48.10%	11	39.30%	0.508
	female	14	51.90%	17	60.70%	
Age (years)		41.89	± 12.28	44.5	± 10.36	0.397
Weight (kg)		76.52	± 6.95	74.82	± 6.14	0.341
BMI		24.41	± 3.209	23.52	± 3.271	0.658
LVEF%		56.26	± 4.147	56.86	± 5.529	0.653
NYHA	ii	21	77.80%	21	75.00%	0.508
	iii	6	22.20%	7	25.00%	

Tab. 2: Surgery/Anesthesia-Related Variables

	propofol			dexmedetomidine			P value
Total midazolam (mg)	7.74	±	0.74	7.75	±	0.66	0.961
Total propofol (mg)	453.20	±	79.45	459.66	±	57.31	0.497
Total Fentanyl (µg/kg)	9.48	±	0.849	9.93	±	0.979	0.076
Operative time (min.)	212.41	±	20.63	205.71	±	22.18	0.252
CPB time (min.)	102.15	±	17.74	98.86	±	18.41	0.503
AXC time (min.)	70.11	±	11.67	66.79	±	11.91	0.301

Tab. 3: Type of Surgery.

Type of surgery	propofol		dexmedetomidine		P value
CABG	9	33.30%	8	28.60%	0.994
Single mitral valve	7	25.90%	8	28.6%	
Single aortic valve	6	22.20%	6	21.40%	
Double mitral and aorta	4	14.80%	5	17.90%	
Combined CABG & valve surgery	1	3.70%	1	3.60%	
Total	27	100.00%	28	100.00%	

As regard number of patients that were considered quit arousable (SAS 3) groups were compared hourly and no intergroup significant difference was shown (tab. 4).

There was a significant difference between propofol and dexmedetomidine as regard total sedation time, this was due to Propofol was stopped immediately before extubation and dexmedetomidine continued for an hour post-extubation (tab.5).

In spite of that Result demonstrated also that there were no significant differences as regard time spent until SAS 4, and time spent at SAS 4 and percentage of time spent at SAS 4 in relation to total sedation time in both groups.

Both groups were similar as regard sedation level compared hourly allover the time of the study (tab. 6). In both groups, patient SAS score never exceed 5 and patients showed good synchronization with mechanical ventilator and there was no need for additional rescue sedation and no failed sedation technique was recorded.

Tab. 4: Number of arousable patients per hour.

Number Patients	propofol	dexmedetomidine	P value
at 1st hour	7 (26%)	8 (29%)	0.827
at 2nd hour	26 (96%)	28 (100%)	0.093
at 3rd hour	27 (100%)	28 (100%)	1

Tab. 5: Primary outcome of the study and sedation related times.

	Propofol		dexmedetomidine		p value
Time spent until SAS 4	208.89	± 50.41	195.00	± 52.67	0.323
Time spent at SAS 4	146.67	± 48.04	143.57	± 49.90	0.816
Total time of sedation	273.33	± 29.48	306.82	± 26.62	<0.001*
The % of time spent at SAS4	54.12%	± 18.61	47.12%	± 16.37	0.144

Tab. 6: Median Sedation Level per hour

SAS score	Propofol		Dexmedetomidine		P value
	Median	IQR	Median	IQR	
at 1st hour	1	1-2	1	1-2	0.827
at 2nd hour	2	2-2	2	2-2	0.093
at 3rd hour	3	3-3	3	3-3.75	1.000
at 4th hour	4	3-4	4	3-4	0.163
at 5th hour	4	3-4	4	4-4	0.250
at 6th hour	4	4-4	4	4-4	0.514

Results showed that no statistically significant difference as regard level of pain throughout the study period (tab. 7). Results demonstrated also that the patients sedated with dexmedetomidine needed less morphine (4.193 mg ± 0.963) than those sedated with propofol compared (9.148 mg ± 2.185) (Fig. 1).

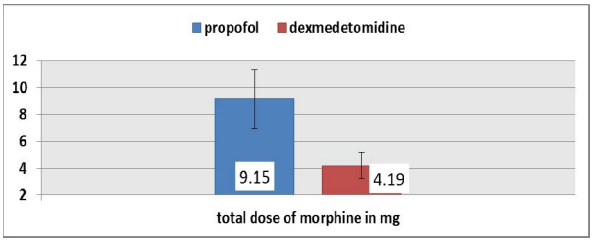

Fig. 1: Total morphine requirements

(Tab. 7): CPOT score

CPOT	Propofol		Dexmedetomidine		p value
	Median	IQR	Median	IQR	
at 1st hour of icu admission	1	0-1	1	0-1	0.225
at 2nd hour of icu admission	2	1-2	1.5	1-2	0.127
at 3rd hour of icu admission	2	2-2	2	2-2	0.716
at 4th hour of icu admission	3	3-3	3	2-3	0.147
at 5th hour of icu admission	3	3-3	3	3-3	0.968
at 6th hour of icu admission	3	3-3	2.5	2-3	0.076

Results showed that time to wean in dexmedetomidine group was significantly shorter than it in propofol group with (p value.021) and mean time difference between groups was 7.68 minutes with 95% CI of difference (1.2-14.1 minutes).

Mean time to extubation in dexmedetomidine patients was statistically significant shorter than for those in propofol group with (p value 0.001) (tab. 8) and mean time difference between groups was 26.5 minutes with 95% C.I. of difference (11.3-41.6 minutes). Median and IQR of weaning time and extubation time of both groups are shown in (fig.2).

Results showed that there was a statistically significant difference as regard total number of extubated patients per hour after ICU admission At 4th hour (p = 0.011) But by the 5th hour post at ICU there was no difference of statistical significance (tab. 9).

(Tab. 8): Mean time to wean and mean time to extubation.

	propofol			dexmedetomidine			p value
Time to wean (min.)	110	±	12.52	103	±	11.34	0.021*
Time to extubation (min.)	273	±	29.65	247	±	26.65	0.001*

(Tab. 9): Total number of extubated patients per hour.

	Propofol	Dexmedetomidine	p value
At 3rd hour	0 (0%)	0 (0%)	_
At 4th hour	4 (14.80%)	13 (46.40%)	0.011*
At 5th hour	25 (92.6%)	28 (100.00%)	0.142
At 6th hour	27 (100.00)%	28 100.00%)	_

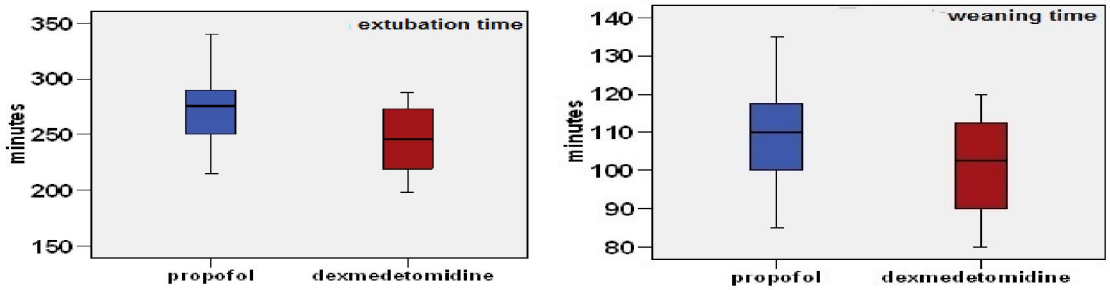

Fig. 2): median and IQR of weaning and extubation times

Dexmedetomidine patients had a significant lower HR than propofol patients, during both sedation on mechanical ventilation and during extubation process (fig.3).

Also, there was significant increase of HR during extubation in propofol group p < 0.001 while dexmedetomidine had more stable HR during extubation with p values > 0.05 at all extubation related times.

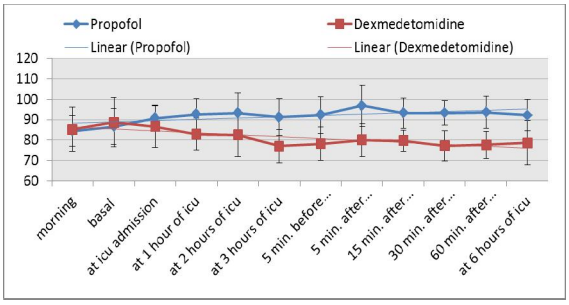

Figure 3: HR trend

Results showed that dexmedetomidine patients had a significant lower MAP than propofol patients, during both sedation on mechanical ventilation and during extubation. Significance was not shown at ICU admission and 1st hour post admission times, despite that dexmedetomidine patients was still had lower MAP than propofol at these times (fig. 4).

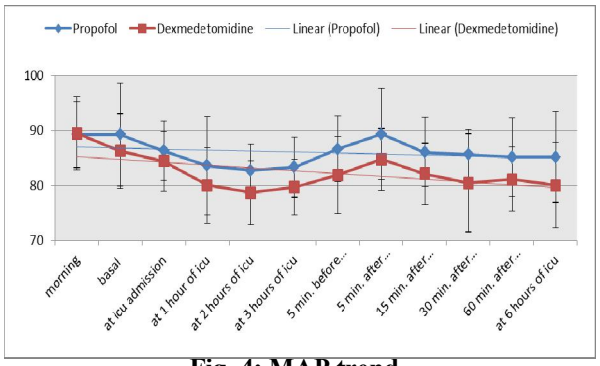

Fig. 4: MAP trend

Adrenaline was the only needed inotropic agent and Results showed that there was no significant difference between both groups as regard it (tab. 10).

Also, no significant difference between groups as regard RR, spo2 and arterial blood gas parameters (pH, PaCo2, p/f ratio and base excess) even after extubation.

The results showed that there were no statistically significant differences between groups as regard serum cortisol and serum glucose at all different times (morning, basal and post extubation) (tab. 11, 12).

Incidence of Shivering was obviously lower in dexmedetomidine group compared to propofol group 2 and 9 cases respectively. Results also, showed that both group had the same incidence of PONV (tab. 13). In both groups No reintubation or accidental self extubation were recorded.

There were significant differences in two group satisfaction assigns as results showed that 12, 19 good and 16, 8 excellent assign for dexmedetomidine and propofol respectively. Result showed significantly superior mean Investigator overall satisfaction rate for dexmedetomidine group than for propofol (fig. 5).

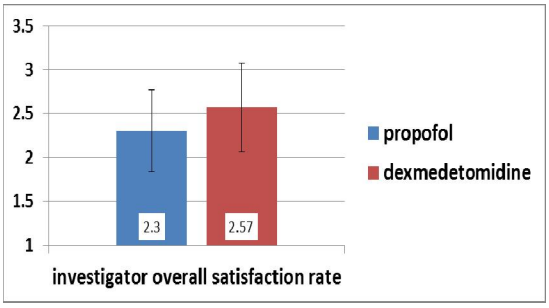

Fig. 5 investigator overall satisfaction

Tab. 10: Inotropic support comparison.

Time	start of sedation		1st hour of icu		2nd		3rd	
group	Prop.	Dex	Prop.	Dex	Prop.	Dex	Prop.	Dex
Number	25	27	26	27	23	22	8	9
infusion rate	71.0	72.2	60.6	62.0	38.0	38.4	31.3	34.4
SD	± 24.7	± 25.3	±14.4	±16.1	±10.5	±10.6	±8.3	±10.4
P value	0.861		0.730		0.908		0.500	

Tab. 11: serum cortisol level

serum cortisol	propofol	dexmedetomidine	p value
morning	12.65 ± 2.10	13.14 ± 2.00	0.379
basal	21.34 ± 3.37	19.64 ± 3.40	0.068
post-extubation 20min.	10.27 ± 2.78	11.30 ± 2.02	0.121

Tab. 12: Serum glucose level

serum glucose	propofol	dexmedetomidine	P value
morning	98.48 ± 18.11	102.75 ± 15.41	0.350
basal	126.33 ± 12.78	131.00 ± 15.02	0.221
post-extubation 20min.	130.30 ± 11.19	128.86 ± 11.75	0.644

Tab. 13: early post-operative complication

	propofol	dexmedetomidine	p value
PONV	1 (3.7%)	1 (3.6%)	0.979
Shivering	9 (33.3%)	2 (7.1%)	0.015*

4. Discussion

Most patients after cardiothoracic surgery and cardiopulmonary bypass (CPB) have markedly increased circulating catecholamines, which may contribute to an initially elevated, labile pulmonary vascular resistance and pressure. The use of adequate sedation and analgesia are important in order to modulate physiological response to stress and pain, reduce cardiovascular instability, and maintain ventilator synchrony hence reducing morbidity and mortality [18].

Both dexmedetomidine and propofol have been recommended as first line agents over benzodiazepines by American College of Critical Care Medicine in the Clinical practice guidelines for the management of pain, agitation, in adult patients in the intensive care unit 2002 and its update in 2013 [10].

Based upon the previous known characteristics of the study drugs, propofol was stopped prior to extubation while dexmedetomidine was continued for 1 hour post extubation in this current study [3] [8] [13].

In this study, we aimed to compare dexmedetomidine based sedation with our standard propofol regime, in order to provide an alternative or better sedation regime to our patients.

The previous studies also, showed that Rapid infusion of loading dose of dexmedetomidine has been associated with a biphasic response, transient hypertension followed by severe hypotension [26]. Activation of peripheral α2-adrenoreceptors in blood vessels mediates vascular smooth muscle contraction, transiently increasing vascular resistance. This is followed by activation of postsynaptic receptors in the central nervous system, which then induces centrally mediated sympatholysis, lowering blood pressure [13].

Large bolus of propofol has also been associated with the occurrence of significant hypotension and bradycardia [24)]. To avoid occurrence of these undesired responses, large rapid loading dose was omitted in both groups in this trial. Also, two issues of interest regarding non double blind design of this study were of concern, that 2 drugs are managed differently and can manifest their results very differently. So the blind itself could result in inappropriate care. Also, because the two drugs have different characteristics, a double-dummy, double-blind design would have been inadequate in the clinical setting.

Average time from starting sedation until arrival to ICU was about 30 minutes. This was considered sufficient for adequate depth of sedation when patients reached ICU, taking into consideration the additive effects of residual intraoperative opioids [37] [16].

All patients when arrived to ICU were intubated and non arousable, with no significant residual muscle relaxation that was confirmed by nerve stimulator. Pain was continuously monitored by CPOT score and vital signs were used only as a cue to begin further assessment of pain. Morphine was the only used analgesic. Analgesia-first sedation (analg-sedation) was used.

Sedation-Agitation Scale (SAS) was used for monitoring depth of sedation. It was simple, easy to remember and reliable. Sedative medications were titrated to maintain a light level of sedation (SAS4).

As regard primary outcome of the study; results demonstrated that dexmedetomidine was not inferior to propofol as regard percentage of time spent at SAS 4. There was no evidence of a significant difference between sedative drugs. It was 54.12% ± 18.61 for propofol and 47.12% ± 16.37 for dexmedetomidine with mean difference 7.00% and 95% of confidence interval of difference (-2.74 to 16.47%) (p=0.144).

A similar result to this study was showed in many trials [28] [44] [19] [29] [24].

In contrast to this study, others [23] [19] [15] demonstrated that propofol resulted in a more comfortable patient experience during mechanical ventilation, with less pronounced sleep difficulties.

The difference in results may be due to different targeted sedation level or range among trials as more light sedation level was targeted in our study. The protocol followed in this trial was different from the other trials in targeting a concise level of sedation SAS 4 as early as possible while level of sedation was a variable parameter (secondary outcome) in other trial. Other studies investigated Satisfaction from Patient point of view as regard amnesia and recall that were not investigated in this trial. All of the previous causes were in line with the heterogeneity in findings of the previous trials as compared with present trial.

Mean infusion rate that was needed to maintain patient calm and co-operative (SAS 4) was 0.39 ± (0.09) µg/ kg/ h for dexmedetomidine and 1.89 ± 0.71 mg /kg/ h for propofol.

In a Total 5 cases during management of adverse effects, infusion rate was reduced to the minimum rate but never stopped. Two cases in propofol group and 3 cases in dexmedetomidine group due to hypotension and or bradycardia that was easily managed by decreasing infusion rate to minimum, lowering head of the bed and optimizing preload. Transient inotropic infusion rate increase was indicated in one of the two propofol cases. Atropine 0.5mg was given in two of the three dexmedetomidine bradycardia event.

Dexmedetomidine has a different type of sedation compared with benzodiazepines and propofol that depends primarily on activation of the gamma aminobutyric acid (GABA) receptors [6]. Sleep like state effect of dexmedetomidine could be explained by

its primary site of action which is the locus coeruleus and not the cerebral cortex [8].

The unusual subcortical action of dexmedetomidine induces sedation that was characterized by an easy and quick arousal, resembling natural sleep "interactive" form of sedation [48].

As regard Pain and Analgesia; the level of pain was always within the acceptable and tolerable level in both groups as it never exceeding (CPOT 4). As regard morphine requirements, patients sedated with dexmedetomidine needed significant lower dose of morphine compared to those sedated with propofol (actually less than the half in propofol group).

This was in line with the already known about pharmacological properties of both study drugs. Propofol has no analgesic effect and led to increase requirements of morphine [17]. On the other hand, dexmedetomidine analgesic effect is due to activation of α 2a adrenoreceptors in the intermediolateral cell column and the substantia gelatinosa of the dorsal horn of the spinal cord inhibits release of substance P (nociceptive mediator), stimulates acetylcholine release in the dorsal horn, attenuates nociceptive signal transduction through A and C fibers and stimulates the release of encephalin-like substances at peripheral sites resulting in primary analgesic effects [20]. This analgesic property of dexmedetomidine is one of its unique features. Other commonly used sedative agents such as midazolam and propofol have no analgesic effect [43].

Similar studies comparing propofol and dexmedetomidine -based sedation therapy in mechanically ventilated cardiac surgery patients showed that dexmedetomidine provides intense analgesia during the postoperative period and reduces the total number of postoperative patients requiring opioids with a corresponding reduction in opioid-associated side effects [7] [4] [9] [49]. This was constant with the finding of previous studies on ICU patients, which demonstrated that dexmedetomidine reduced the use of concurrent analgesia [45] [41] [24].

As regard Weaning and extubation;

Results showed thatdexmedetomidine Patients had statistically significance short time to weaning and short time to extubation than those in propofol group. Study showed that dexmedetomidine produces sedation without the risk of respiratory depression, reduces the hemodynamic response to extubation, so sedation can occur with dexmedetomidine over the extubation period without concern of respiratory depression.

As regard "fast-track" cardiac surgery, 'techniques aim to extubate patients within 6 hours postoperatively', both propofol and dexmedetomidine achieved the task. This is valuable after cardiac surgery as patients ventilatory reserve is impaired by the surgical incision and reliance on mechanical ventilation. Other studies showed same results [39] [12].

In Contrast to this study, studies [45] [7] [13] Comparing dexmedetomidine and propofol for sedation in the cardiothoracic ICU, and in a study Comparing dexmedetomidine and propofol after CABG [24] all showed no significant differences in times of extubation between propofol and dexmedetomidine groups.

This difference in results may refer to the difference in definition of time to extubation between the studies. Time to extubated in our study was defined "minutes, elapsed from patient ICU admission to the point at which patient was considered ready for extubation" while in the other studies time to extubate was "the time elapsed after stop of sedative infusion until patient was extubated" that was considered completely different outcome and only share our outcome in name.

As regard Hemodynamic and respiratory parameters;

All patients of both groups were mechanically ventilated up to the end of the first 3 hours post ICU admission and all patients were extubated by the 6 hour, on contrary, at 4th, 5th hours there was a great variability between both groups and even among patients of the same group as regard intubation status. That was considered would have great impacts on hemodynamic and respiratory parameters and may lead to bias in results interpretation and needs for more complex statistical subgroup analysis. So, hemodynamics and respiratory was compared at morning, basal, 1st, 2nd, 3rd, 6th hours post ICU admission and at times related to extubation.

Dexmedetomidine patients had slower HR than propofol during both sedation on mechanical ventilation and during extubation process. HR in dexmedetomidine group was lowered by time as compared to the basal HR. there was significant increase of HR during extubation in propofol group while dexmedetomidine had more stable HR during extubation.

Dexmedetomidine reduces peripheral catecholamine levels due to its central effect without exerting negative inotropic effect on heart, preventing postoperative myocardial ischemia, thus making dexmedetomidine an attractive choice for cardiothoracic surgery.

Two cases in dexmedetomidine group developed bradycardia. One occurred at 3 hours of ICU admission, Infusion rate was 0.6 µg/ kg /h while other occurred at 50 minute of the post extubation at infusion rate was 0.4µg/kg/h. No cases developed bradycardia in propofol group.

In comparison to propofol Results showed that dexmedetomidine was not associated with significant increased risk of bradycardia requiring interventions p = 0.157. A relatively simple intervention such as reducing the infusion rate was only required and atropine was used once.

The sympathetic activity Modulation that characterizes dexmedetomidine may thus be beneficial in preventing myocardial ischemia. In contrast to β adrenoceptor antagonists, which exert their anti-ischaemic effects directly at adrenergic receptors of the heart, α2-receptor agonists produce a myriad of effects, activation of postsynaptic receptors in the central nervous system reduce central sympathetic nervous system activity (a potential advantage over β blockers), produces a decrease in HR and blood pressure, blunt the hemodynamic variability during sedation and extubation, without exerting negative inotropic effects [38]. Similar Results to this study were demonstrated by [15] [23] [24] [32] [44].

Benefits of heart rate reduction property were reported in previous study showed that Dexmedetomidine increases hemodynamic stability because of attenuation of the stress-induced sympatho-adrenal responses (causing significantly lower plasma norepinephrine levels) and improves graft patency because sympathetic nervous system activation that may play a role in early graft thrombosis secondary to platelet activation [33].

This reduction in heart rate can reduce myocardial oxygen demand and hence subsequent ischemia and infarction. This is of a major importance in critically ill patients, especially during periods of stress e.g. endotracheal suctioning, physiotherapy, and mobilization. Stress is considered to be a major risk factor in myocardial ischemia after surgery [7].

Chrysostomou and collegesconcluded that dexmedetomidine increases coronary blood supply to the left ventricle by prolonging diastolic time, and decreases myocardial oxygen consumption. Thus, endocardial perfusion is preserved and oxygen demand reduced in parallel with oxygen supply and energy requirements, preventing postoperative myocardial ischemia [14].

Previous studies report biphasic response to dexmedetomidine infusion when large loading dose (1μg/kg over 10 minutes) or large doses of infusion > 0.7 μg/kg/h were used. Biphasic response is due to Activation of peripheral α2-adrenoreceptors in blood vessels mediates vascular smooth muscle contraction, transiently increasing vascular resistance. This is followed by activation of postsynaptic receptors in the central nervous system, which then induces centrally mediated sympatholysis, lowering blood pressure and heart rate [50]. In the current study no patient in dexmedetomidine group showed biphasic response with sedation.

As regard mean arterial blood pressure;

Results showed a statistically significant difference in MAP between groups (lower MAP in dexmedetomidine than propofol group) during sedation and during extubation times. For both groups, the mean arterial blood pressures (MAP) values during sedation were significantly lower than basal value (presedation). The results showed that Incidence of hypertension was (3, 1) in propofol and dexmedetomidine respectively with p 0.282 while Incidence of Hypotension was (4, 5) with P value 0.760.

In cases of hypertension infusion rate was increased up to maximum. While in hypotension infusion rated was decreased to minimum in only 2, 3 cases in propofol and dexmedetomidine respectively.

The hypotensive effect of propofol is due to a decrease in systemic vascular resistance, cardiac output, a combination of venous and arterial vasodilatation, impaired baroreflex mechanism, and depression of myocardial contractility [30] [17].

On the other hand, dexmedetomidine reduces blood pressure through stimulation of presynaptic alpha2 adrenergic receptors in the sympathetic nerve endings, inhibiting the release of noradrenaline, activating postsynaptic receptors in the central nervous system, and inhibiting sympathetic activity [40]. Similar results were reported in many trials [1] [24] [44].

On other side, Non- significant differences after cardiac surgery were reported in comparing both drugs [7] [44].

In contrast to this result, **[5]** in a study comparing the efficacy, side effects, and recovery characteristics of dexmedetomidine versus propofol when used for intraoperative sedation demonstrated that patients received propofol had significantly decreased intraoperative MAP levels in comparison to dexmedetomidine. Similar results also showed in a study [2].

The great variability in results of the previous studies may be resorted to heterogeneity among the studies in (type of procedure performed as in Ahmed and college study that was for MRI, type of patients as in Mukhtar and colleges and different time of infusion as **Arain and Ebert** study that compared both drugs in regard to intraoperative sedation).

As regard respiratory rate (RR) and oxygen saturation (Spo2);

No significant difference between groups through the whole study period. Interestingly, even after extubation also, there was no significant difference. In this study Apnea and hypopnea was defined according to apnea-hypopnea indices (AHIs)

that were originally published by American Academy of Sleep Medicine (AASM) hypopnea scoring criteria (AHIChicago). No patient had episodes of serious respiratory depression (apnea) in any of study groups and hypopnea events was managed easily in the current study by decreasing infusion rate to minimal, patients stimulation (tactile or verbal), asking patient to breath and increasing Fio2. These side effects raise the concern about end tidal capnography monitoring that wasn't used in this study and it will be valuable to be used in the sedation related trials.

Dexmedetomidine is not gamma-aminobutyric acid mediated. As such, it produces sedation without the risk of respiratory depression. It converges on the natural sleep pathway to exert its sedative effects. Hypercapnia activates the locus coeruleus, which is associated with increase apprehension leading to stimulation of the respiratory centers [22].

On the other hand, propofol profoundly affected respiratory system by producing a dose dependent depression of ventilation and producing apnea. It inhibits normal response to hypercarbia hypoxic ventilatory drive, and the normal protective respiratory reflexes [34]. It depresses respiration by stimulating central γ- aminobutyric acid (GABA) receptors [35].

Studies reported that dexmedetomidine did not significantly prolong the recovery time of spontaneous breathing and the eye-opening time compared with propofol. However, some patients may have respiratory depression due to the interaction between dexmedetomidine and residual anesthetics and muscle relaxants if used for long period or high extra-clinical doses [31] [27].

Data reported from the previous studies revealed that In a high-dose safety study in volunteers, **Dr. Ebert** and his colleagues demonstrated remarkably well-preserved respiratory parameters and oxygen saturations in volunteers who were essentially unarousable from extremely high doses of dexmedetomidine (8- to 10-fold higher levels than recommended for therapy) [18]. Also **Venn et al** stated that "A sedative agent that has analgesic properties, minimal effects on respiration and may offer ischemia protection would also have enormous potential outside the ICU [45].

Similar to the current result other study concluded that, dexmedetomidine may fulfill all of these roles, but at present we can only conclude that it has no deleterious clinical effects on respiration when used in doses that provide adequate sedation and effective analgesia in the surgical population requiring intensive care" [46].

Similar results was reported in a study of the advantageous effects of dexmedetomidine on hemodynamic and recovery responses during extubation for intracranial surgery, demonstrated that dexmedetomidine improved extubation conditions, and did not prolong recovery [42] similarly **Hsu et al**studyconcluded that compared the respiratory effects of dexmedetomidine and remifentanil in healthy volunteers [25].

As regard arterial blood gas parameters;

Results of the current study showed that, No statistically significant difference ABG parameters (pH, PCo2, base excess and PO2/FiO2) were noted at different times between the both groups even after extubation, Similarly results showed by other studies [46] [36].

All patients received oxygen therapy throughout the study period. So (PaO2: FIO2 ratio) was chosen by the authors as a comparison variable to allows the variation in administered oxygen to patients during the study period.

As regard Endocrine and Inflammatory response parameters (stress response);

Results of the study showed that glucose level and cortisol level were similar in both group and non-significant statistical difference between groups was demonstrated. Results demonstrated also that both groups followed normal circadian rhythm of cortisol level (morning levels were greater than night post-extubation levels) and for both groups, mean presedation level (at end of surgery) also was higher than mean night levels (peak extubation related stress) this may indicate effective sedation level and sufficient analgesia patients had at ICU and demonstrate that study drugs not inhibit steroidogenesis that was considered hazards in icu patients. Similar results showed by a study [19].

Cortisol has widespread effects on the metabolism and utilization of glucose, amino acid and fatty acids in hepatic and extra-hepatic tissues. Cortisol causes rapid mobilization of amino acids and fat from their cellular stores, making them immediately available both for energy production and for synthesis of other compounds including glucose needed by different tissues [51]. In contrast, a study investigated effect of dexmedetomidine intravenous infusion on some proinflammatory cytokines, stress hormones and recovery profile in major abdominal surgery demonstrated that patients who received dexmedetomidine had significantly lower intraoperative cortisol levels as compared with placebo group [51].

A studyinvestigated the effects of dexmedetomidine to attenuate the hemodynamic and neuroendocrine responses to skull-pin head holder application during craniotomydemonstrated that, plasma concentration of cortisol had increased significantly in the placebo group, than in the dexmedetomidine group [43].

As Regard Side Effects; PONV, Reintubation and Shivering;

The intergroup comparison showed that incidence of PONV was comparable between groups and occur once in both groups. No reintubation or accidental self extubation, serious arrhythmias, myocardial infarction, stroke, acute renal failure and mortality had occurred.

In this study Incidence of Shivering was obviously lower in dexmedetomidine group compared to propofol group 2 and 9 cases respectively.

Meperidine was the formal pharmacological treatment used in our hospital for shivering management that was considered may affect pain score and decrease need for morphine and may result in bias of this study, so non-pharmacological management only was allowed in treatment of such cases and if patients developed significant shivering, it was assumed that patient would be excluded if his shivering resort meperidine, but this never occurred in the study. All shivering events was mild, self-limited and there was no need for meperidine.

Shivering in postoperative patients, may increase left ventricular systolic work index and oxygen consumption. Therefore, some simple and inexpensive interventions are effective in the treatment of this adverse effect of anesthesia and surgery [11]. Postoperative shivering is caused by disarray in thermoregulation and could result in significant increases in myocardial oxygen consumption. Dexmedetomidine reduces post anesthetic shivering by inhibiting central thermoregulation control possibly by their activity at α2B receptors in the hypothalamic thermoregulatory center of the brain. Low-dose dexmedetomidine has an additive effect on lowering the shivering threshold [21].

As regard investigator overall satisfaction;

Investigator report many reasons for recommendation of dexmedetomidine this mainly was due to its effective sedative and analgesic effects, maintenance of patients' arousability and cooperativity. This allows neurologic assessments and communication with the patient without interruption of the calming effects of sedation. Reduction of heart rate, and hence myocardial oxygen demand and ability to continue Sedation over the extubation period and provides cardiovascular stability, with a reduction in rate-pressure product over the extubation period.

It was shown that a sedative agent that has analgesic properties and minimal effects on respiration would have enormous potential in the ICU. Dexmedetomidine may fulfill these roles.

Similar result was shown by a study compared Dexmedetomidine and propofol for monitored anesthesia care in the middle ear surgery [47].

Similarly, a study Comparing both drugs for vitreoretinal surgery under subtenon's anesthesiastated **"**Dexmedetomidine at similar sedation levels with propofol was associated with equivalent hemodynamic effects, maintaining an adequate respiratory function, similar time of discharge from PACU, better analgesic properties, similar surgeon's satisfaction, and higher patient's satisfaction" [23].

On the other hand, a study [19] demonstrated that propofolresulted in a more comfortable patients experience duringmechanical ventilation, with less pronounced sleep difficulties. The reason for these results in the previous studies may be the different type of surgery.

Study concluded that;

In provision of sedation for patients scheduled for fast-track cardiac surgery, Dexmedetomidine proved to be an attractive option in comparison to propofol. It was distinctive from propofol in being none GABA mediated. It produces sedation without the risk of respiratory depression even when continued after extubation. It was superior to propofol as regard weaning and extubation times and preventing postoperative shivering.

When compared to other starting loading dose regimens, the study with starting infusion rate of 0.4 µg / kg / hr results in none initial hypertension and it was sufficient quietly to lowers postoperative morphine requirements, heart rate, Mean arterial blood pressure and increase investigators overall satisfaction rate. However, both drugs were comparable as regard other hemodynamics, respiratory parameters and stress response to surgical trauma, mechanical ventilation, extubation process. Also, incidences of hypotension or hypertension, PONV were similar. Finally Dexmedetomidine may be superior to propofol in this patient's population.

Limitation of the current study and Recommendation for further studies;

Due to short period of the study, further long term outcomes studies are recommended. The results could not be generalized to other ICU settings. Further studies are recommended in other major operations (e.g. thoracic, vascular and neurosurgery) and many different groups of patients (e.g. critically ill, septic patients, patients need long term ventilation, airway compromised patients like maxillofacial and obstructive sleep apnea patients also patient at risk of pulmonary or cardiac decompensation). Result of this study couldn't be extrapolated to patients with higher cardiac surgery risk. Studies in this field still not enough and so, further study targeting these high risk patients is required.). Objective measures of brain function (e.g., BIS) will be of a great value as an adjunct to SAS in further studies targeting sedation in ICU. Future studies aiming satisfaction outcomes

should include the patient's perspective of sedation quality as well. However these acceptable limitations, we believe our work will shed more light into the subject and perhaps stimulate more research on this topic.

Disclosures and conflicts of interest

This research was not supported by any funding source and authors declare there is no conflict of interest.

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