



ORIGINAL ARTICLE

Morphine, Midazolam and Dexmedetomidine in the Management of Acute Cardiogenic Pulmonary Edema: Safety and Efficacy

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ABSTRACT

Background: Acute cardiogenic pulmonary edema (ACPE) is a stressful scenario characterized by progressive respiratory failure that can result in cardiorespiratory collapse within minutes, or hours, unless therapeutic action is taken. We aimed to compare Midazolam, Morphine and Dexmedetomidine in ACPE regarding efficacy and safety.

Methods: 84 Adult subjects with clinical diagnosis of ACPE with anxiety and severe dyspnea were included in the present study. The cases have been randomized in a 1:1:1 ratio, group (Mi) midazolam, group (Mo) morphine and group (Dex) dexmedetomidine. We assessed respiratory rate, heart rate, oxygen saturation, systolic blood pressure, and dyspnea score, on arrival (baseline) and 6 hours after admission to evaluate clinical improvement. Bed side echocardiography and Lung ultrasound were done. The clinical improvement during length of Intensive Care Unit (ICU) stay is the primary outcome, while the reporting of Serious Adverse Event (SAE) is considered the main safety endpoint.

Results: There was a statistically insignificant variance among study groups; according to past medical history, chronic treatment, management in emergency department, respiratory rate, oxygen saturation, sedation scale, ejection fraction, diastolic dysfunction, lung ultrasound, on admission & follow up Inferior Vena Cava diameter and laboratory findings, mechanical ventilation, in-hospital Mortality and 30-days Mortality. There was statistically significant diminution in heart rate, ICU stay and Ward stay in Dexmedetomidine Group in comparison with Morphine and Midazolam Groups. There was a statistically significant variance among study groups, regarding ICU and Ward stay. There was a statistically insignificant variance among study groups, regarding complications.

Conclusions: Dexmedetomidine seemed to be of superior advantage over both Morphine, Midazolam regarding ICU stay and Ward stay, however both Morphine and Midazolam revealed an advantage over Dexmedetomidine concerning dyspnea and sedation scales.

Keywords: Morphine; Midazolam; Dexmedetomidine; Acute Cardiogenic Pulmonary Edema

INTRODUCTION

ACPE is a stressful scenario characterized by progressive respiratory failure that can result in cardiorespiratory collapse within minutes or hours, unless therapeutic action is taken [1]. Initial events in ACPE include elevated capillary pressures and hemodynamic pulmonary congestion; thus,

non-invasive ventilation (NIV), diuretics, and vasodilators are key armamentarium for initial management [2].

Morphine is a potent opioid analgesic commonly utilized for the management of acute pain and for long-term treatment of severe pain [3] morphine has an affinity for delta, mu-opioid and kappa receptors [4]. This

medication produces most of its analgesic effects by binding to the mu-opioid receptor within the peripheral nervous system (PNS) and the central nervous system (CNS) [5], producing vasodilatation. Morphine was utilized for decades in cases developing acute cardiogenic pulmonary edema because it diminishes anxiety and dyspnea and improves the vasoconstriction accompanying hypertensive crises [6].

Midazolam is a familiar agent frequently utilized in the emergency department to give sedation before procedures like dislocation diminution and laceration repair. Midazolam is efficient in treating generalized seizures, behavioral emergencies, and status epilepticus [7]. The mechanism of action of midazolam is indirect and associated with Gamma-Amino-Butyric Acid (GABA) accumulation and its affinity for benzodiazepine receptors. 2 separate receptors for GABA and benzodiazepine couple to a common chloride channel [8].

Alternative methods emphasizing agents that provide instantaneous anxiolytic effect with minimal respiratory depression (e.g., midazolam) might be beneficial. Benzodiazepines were utilized as safe anxiolytic medications for decades, and certain authors have recommended that they might be an alternative to morphine in the management of acute cardiogenic pulmonary edema [4, 9]. Midazolam's role in ACPE, Anxiolysis and sedation: It provides an anxiolytic and light sedation effect to help patients cope with the stress and severity of ACPE. Improving NIV compliance: By reducing breathlessness, midazolam helps patients tolerate non-invasive ventilation (NIV), a key treatment for ACPE.

Reduced adverse events: Compared to morphine, midazolam has been associated with fewer serious adverse events in patients with ACPE. Alternative to morphine: Studies suggest midazolam is a safer alternative to morphine for managing breathlessness in ACPE, as morphine has been linked to an increased need for ventilation [9].

Dexmedetomidine is a highly selective α_2 -adrenoceptor agonist. It has analgesic, sedative, and opioid-sparing influences and is

suitable for long- and short-term sedation in an intensive care setting [10]. Although literature is limited, there is proof supporting dexmedetomidine for cases unable to tolerate NIV, particularly among cases had cardiogenic pulmonary edema. It seems to have a good safety profile when utilized as the sole sedative agent. Acute cardiogenic pulmonary edema involves significant sympathetic nervous system activation, which can worsen cardiac function by increasing heart rate and blood pressure. Dexmedetomidine, an α_2 -adrenergic agonist, reduces this sympathetic tone, leading to a decrease in cardiac workload. Patients with ACPE can be anxious and agitated, making it difficult to tolerate a tight-fitting NIV mask. Dexmedetomidine provides light, "cooperative" sedation that allows them to tolerate the mask and therapy [10].

Previous studies used one of these medications or compared two of them, so the present study was designed to compare the three medications regarding safety and efficacy.

Objectives of the study

The present research has been carried out to compare Midazolam, Morphine and Dexmedetomidine in ACPE regarding efficacy and safety. The present research has been performed at Menoufia University Hospital and Damietta Cardiology Center, on adult subjects with clinical diagnosis of acute cardiogenic pulmonary edema with anxiety and severe dyspnea.

Primary outcome measure was the Clinical improvement in length of hospital stays.

Secondary outcome measures were the need for invasive mechanical ventilation, In-hospital all-cause mortality and 30-day mortality.

METHODS

After receiving ethical approval from the Menoufia University Research Committee and department of Anesthesia and Intensive Care Unit under IRB number (3/2024 ANET10), this prospective, controlled, double blind, randomized trial, was conducted from April 2024 to December 2024. Retrospectively registered in the Clinical Trials.gov ID (NCT06653244) on 13-10-

2024. Performed as per the principles of the Helsinki Declaration. Each participant provided written informed consent. Our study adheres to CONSORT guidelines.

The study included Patients older than 18 years old with a clinical diagnosis of acute cardiogenic pulmonary edema with severe dyspnea and anxiety. The diagnosis confirmed by echocardiography that revealed impaired left ventricular systolic function, diastolic dysfunction, dilated non collapsable inferior vena cava (IVC) and the lung US revealed B-Lines > 30. Diagnosis of acute cardiogenic pulmonary edema has been described by the correlation of sudden onset of dyspnea, bilateral rales on auscultation, respiratory rate above twenty-five breaths/minute and pulse oxygen saturation below ninety percent on room air [11].

The study excluded patients with history of severe stenotic heart disease, Cardiovascular collapse or an impaired level of consciousness, Immediate indication of intubation, Suspicion of acute coronary syndrome, Known severe liver disease, renal disease, or pneumonia, Psychiatric disorders.

Randomization was conducted by a computer-generated program into three equal parallel groups that were randomly assigned, each group included 28 cases. The cases have been randomized in a 1:1:1 ratio, group (Mi) midazolam (administered intravenously at a dosage of one milligram, as much as a maximum dose of three milligrams), group (Mo) morphine (administered intravenously at a dosage of two to four milligrams, as much as a maximum dose of eight milligrams, and group (Dex.) dexmedetomidine (administered intravenously, Load: 0.25 micrograms per kilogram IV over ten minutes, Maintenance 0.2-0.7 micrograms per kilogram per hour continuous IV infusion according to hemodynamics and sedation score of patient, not to exceed 12 hr. In acute cardiogenic pulmonary edema, midazolam and morphine are given as boluses to provide rapid relief from anxiety and dyspnea, while dexmedetomidine is given as an infusion because it provides longer-lasting, continuous sedation with minimal respiratory depression and may offer additional benefits like

reducing pulmonary congestion. The bolus approach allows for immediate, on-demand treatment, whereas the infusion ensures a steady level of sedation suitable for longer-term management, such as during non-invasive ventilation.

Ethical Considerations

The research was conducted from April 2024 to December 2024 after Approval form ethics committee was obtained. Confidentiality and privacy have been respected at all levels. Written informed consent has been taken from each case enrolled in, or first-degree relatives.

All cases have been admitted to CCU, had I.V lines, central venous catheters and were attached to monitors to show their blood pressure, heart rate and oxygen saturation. The respiratory distress and anxiety were assessed utilizing a Modified Borg Dyspnea scale (Figure 1) varying from 0 (no breathlessness) to 10 (maximum breathlessness) [12], on admission and after 6 hours. All patients were assessed for need of non-invasive ventilation by Continuous Positive Airway Pressure (CPAP.)

Basic management with intravenous infusions of nitroglycerine, intravenous boluses of loop diuretics, oxygen supplementation have been given by doctors as regards their clinical judgment. The target in all cases was clinical improvement by providing anxiolytic or light sedation effects for good compliance with non-invasive ventilation and reducing pulmonary congestion. The expected sedation scores (Ramsay score 2-3) (Figure FS1) have been evaluated in all cases taking morphine, midazolam or dexmedetomidine after 6 hours. Collected Data (on admission & after 6 hours). The follow up was continuous as any critical case but the documented assessment which was written to see the effect of the three drugs in first critical hours in ACPE with this time interval to see the impact of these drugs.

We assessed vital signs such as respiratory rate, heart rate, oxygen saturation, sedation score, dyspnea score and systolic blood pressure on arrival and 6 hours after

admission to evaluate clinical improvement. Bed side echocardiography was done to show left ventricular systolic function, diastolic dysfunction that ranged from 1 to 4 and IVC diameter for assessment of clinical improvement and decrease of pulmonary Lung ultrasound was done in all patients on admission to confirm diagnosis of cardiogenic pulmonary edema as presence of B-lines more than 30 with echo findings was enough for confirmation. It was repeated in follow up especially after 6 hours. The significant decrease of B-lines to 10 or less was considered a clinical improvement sign.

Study Outcomes

The present study assessed the efficacy and safety of Morphine, Midazolam and Dexmedetomidine in patients with ACPE. The reporting of Serious Adverse Event (SAE) is deemed the primary safety endpoint. A SAE including need of mechanical ventilation, in-hospital mortality and thirty days death. Cardiovascular, respiratory, neurological and renal complications were assessed in all groups.

Efficacy assessment evaluated clinical improvement during length of hospital stay.

Statistical Analysis

Based on review of past literature [19] who found that the dexmedetomidine managed cases additionally illustrated a shorter Intensive Care Unit stay than that treated with midazolam

(4.9 ± 4.3 h vs. 8.5 ± 4.6 h, p-value equal 0.042). The least sample size calculated using statistics and sample size pro is 25 participants per group and increase up to 28 participants per group to avoid 10% drop out rate with total sample size is 84 participants. The power of study is 80% with 95% confidence interval.

The information gathered has been tabulated & analyzed utilizing SPSS (statistical package for the social science software) statistical package version 26 on IBM compatible computer. Descriptive statistics have been represented percentage and number (% & No) for qualitative information, mean ($\bar{x}$) & standard deviation (SD) and range for quantitative information. Chi-squared test (χ^2) has been utilized to study the correlation

congestion. it was measured in all patients on admission and 6 hours after initiation of drugs. Laboratory data included assessment of sodium, potassium, creatinine, and arterial blood gases.

among qualitative parameters. Monte Carlo test has been applied to study the correlation among qualitative parameters if any of the expected cells is below 5. One Way ANOVA test (F) has been applied for comparison of quantitative parameters among above 2 groups of normally distributed information with a Post Hoc test. Kruskal Wallis test (H) has been applied for comparison of quantitative parameters among above 2 groups of not normal distributed information with a Post Hoc test. Paired t test to compare variant readings of normally distributed information in the same group. P value < 0.05 was set to be statistically significant

RESULTS

90 cases have been enrolled in this randomized trial, two patients were excluded due to need of immediate intubation, two were excluded due to suspicion of myocardial infarction and two were excluded due to co-existing pneumonia. The remaining eighty-four participants were allocated randomly into three equal groups (Figure FS2).

All patients were included until the conclusion of the study .57.1 % were males, 42.9 % were females, with mean of age: 69.76 ± 5.62 ranged between 49-80 years. Table (1) demonstrates that there was a statistically insignificant variance among study groups, according to past medical history, chronic treatment, management in emergency department and Vital signs. Table 1 shows the presence of loop diuretics, Beta-blockers, RAAS inhibitors (renin- angiotensin-aldosterone inhibitors). Table 2 shows There was a statistically insignificant variance between study groups: regarding vital signs on admission.

As shown in Table 3 statistically significant variance among study groups; as regards SBP, HR, DBP, and Dyspnea scale 6 hours after providing drugs.

This table shows a statistically insignificant variance among study groups; as regards RR,

SpO₂ and sedation scale. Regarding HR there was statistically significant diminution in Dex. Groups than Morphine and Midazolam Groups. Regarding SBP, there was statistically significant diminution in Morphine Group more than in Dex Group as shown in (Figure FS3).

Regarding Dyspnea scale there was statistically significant reduction in Midazolam Group more than Dex Group (Figure FS4).

Morphine Group: There was statistically significant variance among admission and monitoring; regarding all vital signs.

Midazolam Group: There was statistically significant variance among admission and monitoring; regarding all vital signs except DBP.

Dex Group: There was statistically significant variance among admission and monitoring; regarding all vital signs except DBP (Table 4).

There was a statistically insignificant variance among study groups; as regards EF, Diastolic Dysfunction, on admission IVC and Follow up IVC. There was a statistically insignificant variance among study groups as regards admission and Follow up Lung US (Table 5). There was statistically significant variance (improvement) among on admission and

monitoring IVC in all study groups and statistically significant variance (improvement) among on admission and monitoring Lung US in all study groups (Table 6).

Table TS1 shows a statistically insignificant variance among study groups; according to admission routine laboratory findings in CCU patients, Table TS2 shows a statistically insignificant variance among study groups; according to follow up laboratory findings. Table TS3 shows statistically significant difference in each study group; regarding admission and follow up laboratory findings, except Creatinine. Table TS4 shows statistically significant variance among study groups, regarding ICU and Ward stay. Also shows a statistically insignificant variance among study groups; regarding Mechanical Ventilation, In-Hospital Mortality and 30-days Mortality. Regarding hospital stay there was statistically significant decrease in ICU and Ward stay in Dex Group more than Morphine and Midazolam Group. Figure FS3 shows Boxplot of length of hospital stay among studied groups. Table TS5 shows a statistically insignificant variance among study groups, according to complications.

Table (1): Demographic, clinical information of the examined groups

Parameter	Morphine Group (n=28)	Midazolam Group (n=28)	Dexmedetomidine Group (n=28)	Total (n=84)	Test of significance	P value
	No. (%)	No. (%)	No. (%)	No. (%)		
Sex					$\chi^2=4.67$	0.097
Male	12 (42.9)	20 (71.4)	16 (57.1)	48 (57.1)		
Female	16 (57.1)	8 (28.6)	12 (42.9)	36 (42.9)		
Age (Years)					F=0.25	0.778
Mean $\pm$ SD	70.04 $\pm$ 5.19	69.14 $\pm$ 6.45	70.11 $\pm$ 5.28	69.76		
Range	58-79	49-79	60-80	$\pm$ 5.62		
				49-80		
Hypertension	21 (75)	25 (89.3)	21 (75)	67 (79.8)	$\chi^2=2.36$	0.307
DM	15 (53.6)	18 (64.3)	13 (46.4)	46 (54.8)	$\chi^2=1.83$	0.401
HF	28 (100)	28 (100)	27 (96.4)	83 (98.8)	$\chi^2=2.02$	^{MC} 1.000
AF	2 (7.1)	1 (3.6)	2 (7.1)	5 (6)	$\chi^2=0.43$	^{MC} 1.000
Hypothyroidism	4 (14.3)	1 (3.6)	0 (0)	5 (6)	$\chi^2=5.53$	^{MC} 0.122
Loop diuretics	21 (75)	22 (78.6)	21 (75)	64 (76.2)	$\chi^2=50.13$	1.000
Beta-blockers	26 (92.9)	26 (92.9)	25 (89.3)	77 (91.7)	$\chi^2=50.31$	^{MC} 1.000
RAAS inhibitors	23 (82.1)	25 (89.3)	18 (64.3)	66 (78.6)	$\chi^2=5.52$	0.063
Calcium antagonists	22 (78.5)	24 (85)	17 (60.7)	63 (75)	$\chi^2=4.95$	0.084
Nitrates	7 (25)	2 (7.1)	6 (21.4)	15 (17.9)	$\chi^2=3.40$	0.182
Management/ ED					$\chi^2=11.86$	^{MC} 0.281
None	1 (3.6)	4 (14.3)	2 (7.1)	7 (8.3)		
I.V Diuretics + O ₂ mask	19 (67.9)	21 (75)	25 (89.3)	65 (77.4)		
I.V Diuretics+ Nebulizer + O ₂ mask	3 (10.7)	2 (7.1)	1 (3.6)	6 (7.1)		
I.V Diuretics + Nebulizer	2 (7.1)	0 (0)	0 (0)	2 (2.4)		
I.V Diuretics + CPAP	2 (7.1)	1 (3.6)	0 (0)	3 (3.6)		
I.V Diuretics + O ₂ mask+ CPAP	1 (3.6)	0 (0)	0 (0)	1 (1.2)		

SD: Standard deviation, χ^2 : Chi-squared test, F: One Way ANOVA test, MC: Monte Carlo test,

DM: Diabetes Mellitus, HF: Heart Failure, AF: Atrial Fibrillation, RAAS: Renin-Angiotensin- Aldosterone System,

ED: Emergency Department, CPAP: Continuous Positive Airway Pressure

This study included 84 participants; 57.1 % were males, 42.9 % were females, with mean of age: 69.76 $\pm$ 5.62 ranged between 49-80 years. The presence of hypertension, DM, HF, AF and Hypothyroidism were 79.8 %, 54.8 %, 98.8 %, 6 % and 6 % among study participants respectively. The presence of loop diuretics, Beta-blockers, RAAS inhibitors, Calcium antagonists and Nitrates were 76.2 %, 91.7 %, 78.6 %, 10.7 % and 17.9 % among study participants respectively. Most study participants received I.V Diuretics + O₂ mask in emergency department. This table demonstrates that there was a statistically insignificant variance among study groups, regarding past medical history, chronic treatment and management in emergency department.

Table (2) shows Vital signs on admission of the examined groups

Parameter	Morphine Group (n=28)	Midazolam Group (n=28)	Dexmedetomidine Group (n=28)	Test of significance	P value
HR (Beat/min) Mean± SD Range	111.04 ±7.20 100-130	115.11 ±9.17 104-145	110.54 ±8.50 102-130	F=2.54	0.085
RR (Cycle/min) Mean± SD Range	29.86 ±3.30 25-39	29.43 ±3.45 24-39	28.82 ±2.83 23-37	F=0.74	0.480
SBP (mmHg) Mean± SD Range	106.79 ±7.72 90-120	111.79 ±7.72 100-130	109.64 ±7.44 100-120	F=3.03	0.054
DBP (mmHg) Mean± SD Range	66.07 ±5.67 60-80	69.29 ±7.16 60-80	68.93 ±8.32 60-80	F=1.71	0.188
SO ₂ (%) Mean ± SD Range	86.71 ±3.50 75-92	86.00 ±3.71 75-90	87.11 ±3.11 79-91	F=0.74	0.479
Dyspnoea scale Mean ± SD Range	7.07 ±0.66 6-8	7.00 ±0.82 4-8	6.96 ±0.79 6-9	F=0.14	0.866
Sedation scale Mean± SD Range	1.00 ±0.00 1-1	1.00 ±0.00 1-1	1.00 ±0.00 1-1	----	----

HR: Heart Rate, RR: Respiratory Rate, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, SO₂: Oxygen Saturation

This table illustrates that there was a statistically insignificant variance between study groups, regarding vital signs on admission.

Table (3): Vital signs 6 hours after providing drug among studied groups (n=84)

Parameter	Morphine Group (n=28)	Midazolam Group (n=28)	Dexmedetomidine Group (n=28)	Test of significance	P value	Post Hoc test
HR (Beat/min) Mean± SD Range	98.64 ±8.77 85-125	100.32 ±7.26 87-116	91.11 ±10.35 78-115	F=8.55	<0.001*	P1=1.000 P2=0.006* P3=0.001*
RR (Cycle/min) Mean± SD Range	23.11 ±3.31 18-31	21.86 ±3.22 18-28	22.32 ±3.68 16-32	F=0.96	0.386	----
SBP (mmHg) Mean± SD Range	99.64 ±5.76 80-110	101.43 ±4.48 90-110	104.29 ±6.90 90-120	F=4.57	0.013*	P1=0.758 P2=0.011* P3=0.207

Parameter	Morphine Group (n=28)	Midazolam Group (n=28)	Dexmedetomidine Group (n=28)	Test of significance	P value	Post Hoc test
DBP (mmHg) Mean± SD Range	63.21 ±5.48 50-70	66.43 ±4.88 60-70	66.07 ±4.97 60-70	F=3.32	0.041*	P1=0.064 P2=0.120 P3=1.000
SO₂ (%) Mean± SD Range	94.68 ±3.15 82-98	94.89 ±2.01 89-98	93.68 ±2.93 83-97	F=1.57	0.215	----
Dyspnea scale Mean± SD Range	3.68 ±0.91 3-7	3.18 ±0.67 2-4	3.71 ±0.71 3-6	F=4.25	0.018*	P1=0.052 P2=1.000 P3=0.033*
Sedation scale Mean± SD Range	2.04 ±0.33 1-3	2.18 ±0.39 2-3	2.25 ±0.44 2-3	F=2.19	0.118	----

*: Statistically significant, P1: P value between Morphine Group and Midazolam Group, P2: P value between Morphine Group and Dexmedetomidine Group, P3: P value between Midazolam Group and Dexmedetomidine Group

HR: Heart Rate, **RR:** Respiratory Rate, **SBP:** Systolic Blood Pressure, **DBP:** Diastolic Blood Pressure, **SO₂:** Oxygen Saturation

This table shows statistically significant variance among study groups; as regards SBP, HR, DBP, and Dyspnea scale 6 hours after providing drugs. This table shows a statistically insignificant variance among study groups; as regards RR, SO₂ and sedation scale. Regarding HR there was statistically significant diminution in Dex. Group than Morphine and Midazolam Groups. Regarding SBP, there was statistically significant diminution in Morphine Group more than in Dex Group. Regarding Dyspnea scale there was statistically significant reduction in Midazolam Group more than Dex Group.

Table (4): On admission and follow up vital signs and laboratory findings in each studied group (n=84)

Parameter	Morphine Group (n=28)			Midazolam Group (n=28)			Dexmedetomidine Group (n=28)		
	On admission	Follow up	P value	On admission	Follow up	P value	On admission	Follow up	P value
HR (Beat/min) Mean± SD Range	111.04 ±7.20 100-130	98.64 ±8.77 85-125	<0.001*	115.11 ±9.17 104-145	100.32 ±7.26 87-116	<0.001*	110.54 ±8.50 102-130	91.11 ±10.35 78-115	<0.001*
RR (Cycle/min) Mean± SD Range	29.86 ±3.30 25-39	23.11 ±3.31 18-31	<0.001*	29.43 ±3.45 24-39	21.86 ±3.22 18-28	<0.001*	28.82 ±2.83 23-37	22.32 ±3.68 16-32	<0.001*
SBP (mmHg) Mean± SD Range	106.79 ±7.72 90-120	99.64 ±5.76 80-110	<0.001*	111.79 ±7.72 100-130	101.43 ±4.48 90-110	<0.001*	109.64 ±7.44 100-120	104.29 ±6.90 90-120	<0.001*
DBP (mmHg)			0.030*			0.058			0.058

Parameter	Morphine Group (n=28)			Midazolam Group (n=28)			Dexmedetomidine Group (n=28)		
	On admission	Follow up	P value	On admission	Follow up	P value	On admission	Follow up	P value
Mean± SD	66.07 ±5.67	63.21 ±5.48		69.29 ±7.16	66.43 ±4.88		68.93 ±8.32	66.07 ±4.97	
Range	60-80	50-70		60-80	60-70		60-80	60-70	
SO2 (%)			<0.001*			<0.001*			<0.001*
Mean± SD	86.71 ±3.50	94.68 ±3.15		86.00 ±3.71	94.89 ±2.01		87.11 ±3.11	93.68 ±2.93	
Range	75-92	82-98		75-90	89-98		79-91	83-97	
Dyspnoea scale			<0.001*			<0.001*			<0.001*
Mean± SD	7.07 ±0.66	3.68 ±0.91		7.00 ±0.82	3.18 ±0.67		6.96 ±0.79	3.71 ±0.71	
Range	6-8	3-7		4-8	2-4		6-9	3-6	
Sedation scale			<0.001*			<0.001*			<0.001*
Mean± SD	1.00 ±0.00	2.04 ±0.33		1.00 ±0.00	2.18 ±0.39		1.00 ±0.00	2.25 ±0.44	
Range	1-1	1-3		1-1	2-3		1-1	2-3	

There was statistically significant variance among admission and monitoring; regarding all vital signs in Morphine Group, In Midazolam Group, there was statistically significant variance among admission and monitoring; regarding all vital signs except DBP while in Dex Group there was statistically significant variance among admission and monitoring; regarding all vital signs except DBP.

Table (5): Echocardiography and Lung US findings among studied groups (n=84)

Parameter	Morphine Group (n=28)	Midazolam Group (n=28)	Dexmedetomidine Group (n=28)	Test of significance	P value
EF (%) on admission Mean± SD Range	47.86 ±5.99 35-58	46.07 ±8.21 25-57	45.36 ±9.07 25-58	F=0.75	0.476
Diastolic Dysfunction (No& %) Grade I Grade II Grade III	12 (42.9) 11 (39.3) 5 (17.9)	7 (25) 17 (60.7) 4 (14.3)	8 (28.6) 18 (64.3) 2 (7.1)	$\chi^2=4.70$	^{MC} 0.323
On admission IVC Diameter (cm) Mean± SD Range	2.84 ±0.23 2.3-3.3	2.87 ±0.17 2.5-3.2	2.73 ±0.25 2.1-3.3	F=3.06	0.052
Follow up IVC Diameter (cm) Mean± SD Range	2.51 ±0.22 1.9-2.9	2.53 ±0.15 2.2-2.8	2.40 ±0.26 2.1-3.2	F=3.05	0.053
On admission B-lines >30	28 (100)	28 (100)	28 (100)	----	---

Follow up					
B-lines <10	7 (25)	11 (39.3)	10 (35.7)	$\chi^2=2.05$	0.724
B-lines 10	6 (21.4)	3 (10.7)	4 (14.3)		
B-lines >10	15 (53.6)	14 (50)	14 (50)		

EF: Ejection Fraction, IVC: Inferior Vena Cava,

There was a statistically insignificant variance among study groups; as regards EF, Diastolic Dysfunction, on admission IVC and Follow up IVC. There was a statistically insignificant variance among study groups as regards admission and Follow up Lung US.

Table (6): On admission and follow up ECHO and lung US findings in each group (n=84)

Parameter	Morphine Group (n=28)			Midazolam Group (n=28)			Dexmedetomidine Group (n=28)		
	On admission	Follow up	P value	On admission	Follow up	P value	On admission	Follow up	P value
IVC Diameter (cm)									
Mean± SD	2.84 ±0.23	2.51 ±0.22	<0.001*	2.87 ±0.17	2.53 ±0.15	<0.001*	2.73 ±0.25	2.40 ±0.26	<0.001*
Range	2.3-3.3	1.9-2.9		2.5-3.2	2.2-2.8		2.1-3.3	2.1-3.2	
Lung US									
B-lines <10	0 (0)	7 (25)	<0.001*	0 (0)	11 (39.3)	<0.001*	0 (0)	10 (35.7)	<0.001*
B-lines 10	0 (0)	6 (21.4)		0 (0)	3 (10.7)		0 (0)	4 (14.3)	
B-lines >10	28 (100)	15 (53.6)		28 (100)	14 (50)		28 (100)	14 (50)	

IVC: Inferior Vena Cava, Lung US: Lung Ultrasound

This table shows statistically significant variance (improvement) among admission and monitoring IVC in all study groups. This table shows statistically significant variance (improvement) among on admission and monitoring Lung US in all study groups.

MODIFIED DYSPNEA SCALE	
0	None
0.5	Very, Very Slight (just noticeable)
1	Very Slight
2	Slight
3	Moderate
4	Somewhat Severe
5	Severe
6	
7	Very Severe
8	
9	Very, Very Severe (almost maximal)
10	Maximal

Figure (1): Modified Borg Dyspnea scale

DISCUSSION

ACPE is a stressful scenario with progressive respiratory failure that can result in cardiorespiratory collapse within minutes, or hours, unless therapeutic action is taken [13, 14]. Morphine was utilized for numerous decades in cases of acute pulmonary edema (APE) because of the drug's anxiolytic and vasodilatory features. The non-specific depression of the central nervous system is probably the most significant factor for hemodynamic alterations in APE. Retrospective investigations have demonstrated negative and neutral influences in cases had APE, and therefore certain authors recommend benzodiazepines as an alternate management. The application of intravenous morphine for the management of acute pulmonary edema still controversial [15]. The cases have been randomized in a 1:1:1 ratio, (group Mi) midazolam (administered intravenously at a dosage of one milligram, as much as a maximum dose of three milligrams), (group Mo) morphine (administered intravenously at a dosage of two to four milligrams, as much as a maximum dose of eight milligrams), (group Dex.) dexmedetomidine (administered intravenously, Load: 0.25 micrograms per kilogram IV over ten minutes, Maintenance 0.2-0.7 micrograms per kilogram per hour continuous IV Infusion according to hemodynamics and sedation score of patient ; not to exceed 24 hr), all drugs were introduced in the same diluted volume. Regarding the demographic and clinical data, 84 participants were included in the present study; 57.1 % were males, 42.9 % were females, with mean of age: 69.76 ± 5.62 . The presence of loop diuretics, Beta-blockers, RAAS inhibitors, Calcium antagonists and Nitrates were 76.2 %, 91.7 %, 78.6 %, 10.7 % and 17.9 % among study participants respectively. Most study participants received I.V Diuretics + O₂ mask in emergency department. There was a statistically insignificant variance among study groups; as regards past medical history, chronic treatment and management in emergency department.

In terms of the hemodynamic parameters, the current research demonstrated that there was a statistically significant variance among study groups; according to SBP, HR, DBP, and Dyspnea scale 6 hours after providing drugs. A statistically insignificant variance was detected among study groups; according to RR, SpO₂ and sedation scale. Regarding HR there was statistically significant diminution in Dex group than Morphine and Midazolam Groups. Regarding SBP, there was statistically significant reduction in Morphine Group more than in Dex Group. Regarding Dyspnea scale there was statistically significant decrease in Midazolam Group more than Dex Group.

In agreement with our study, **Domínguez-Rodríguez *et al.***, [17] displayed that the cases stated their degree of dyspnea on a visual analogue scale varying from 0 (no breathlessness) to 10 (maximal breathlessness) at recruitment and no variances have been observed among groups.

Domínguez-Rodríguez *et al.*, [17] believe that morphine shouldn't be routinely utilized for acute chronic pulmonary edema and may be replaced with midazolam for the control of patient anxiety and dyspnea. Consequently, our findings could reinforce current HF suggestions, that routine utilize of opiates in acute HF isn't suggested. The research's strengths involved blind endpoint adjudication and the recruitment of critically diseased cases.

Also, **Huang and his colleagues** [19] revealed that although more dexmedetomidine-treated cases developed bradycardia (18.2 percent against 0, p equal 0.016), no cases needed an intervention or interruption of study medication infusion.

Concerning dyspnea and sedation scale, the current research demonstrated that statistically insignificant differences were recorded between the three studied groups before treatment, while after treatment the three examined groups demonstrated significant improvement compared to before treatment. In addition, there were statistically significant variances between the three studied groups and each other's and between morphine and dexmedetomidine, while no

significant difference was recorded between midazolam and morphine and between midazolam and dexmedetomidine.

Huang *et al.*, [19] conducted their study to compare dexmedetomidine and midazolam for the sedation of cases had NIV and displayed that the expected sedation scores (Ramsay score 2-3) were achieved in all the cases taking dexmedetomidine or midazolam with non-significant variance.

Regarding outcome (efficacy) among studied groups, dexmedetomidine group was associated with significant decreases in both ICU stay and ward stay in comparison with morphine and midazolam groups ($P>0.05$), while insignificant variances were recorded as regards mechanical ventilation, in-hospital Mortality and 30-days Mortality.

In agreement regarding dexmedetomidine, **Lewis *et al.***, [16] conducted their study on 12 RCTs who were included in their final analysis on critically ill cases ($n = 738$ patients), mean age 61.5 ± 6.8 years. On average 36.1 of participants were females. They assessed pooled relative risks (PRs) for dichotomous results and mean differences (MDs) for continuous results with the corresponding ninety-five percent Cis utilizing a random effect model. The utilize of dexmedetomidine, in comparison with other sedation strategies or placebo, reduced the risk of intubation, delirium, and ICU length of stay.

Domínguez-Rodríguez *et al.*, [17] demonstrated that the 1st endpoint of in-hospital all-cause death happened in 12.7 percent of the cases in the midazolam group and 17.9 percent of the cases in the morphine group. Similarly, no variances have been observed among groups in thirty days death, the rate of invasive mechanical ventilation, or the length of hospitalization. The rate of non-invasive mechanical ventilation was comparable between groups (forty [72.7 percent] cases in the midazolam arm and forty-five [80.4 percent] in the morphine arm; p equal 0.37).

Huang *et al.*, [19] demonstrated that when in compression with the group treated with midazolam, the overall period of ICU hospitalization in the group managed with

dexmedetomidine was markedly decreased, ($p=0.010$).

On the contrary, they were against the current study regarding MV, as they displayed that the overall duration of mechanical ventilation in the group managed with dexmedetomidine was markedly reduced, and weaning from mechanical ventilation was easier (p equal 0.042). They were against our study regarding this point as they conducted their study on elderly patients with marked hypoxemia with significant co-morbidities.

Also, **Witharana *et al.***, [18] conducted their research to detect the impact of morphine utilize in acute cardiogenic pulmonary edema on death results. They conducted their research on 6 observational research out of the seventy- three publications recognized were eligible for the meta-analysis giving a total sample size of 152,859 (mean age seventy-five, males forty-eight percent). Of these, four were retrospective analyses. The utilization of morphine in acute cardiogenic pulmonary oedema has been correlated with an increased rate of in-hospital mortality, increased need for invasive ventilation ($p<0.00001$).

Regarding safety, the present study demonstrated insignificant variances among the 3 examined groups according to cardiovascular, respiratory, neurological and renal complications and number of SAE ($P>0.05$).

Tellor *et al.*, [20] conducted retrospective single-center co-heart research on seventy-five mechanically ventilated adults received dexmedetomidine infusion. Cases involved in the study were aged not less than eighteen years; mechanically ventilated for above twenty-four hours; received dexmedetomidine infusion for not less than one hour following above twenty-four hours of continuous infusions of midazolam, fentanyl or propofol. Regarding mechanical ventilation, based on a further analysis of the causes of ETI, the most frequent causes correlated with sedation involved copious airway secretion and vomiting. Ideal sedation with less significant respiratory depression and easier arousal would help cases to discharge their secretions and prevent aspiration, ultimately resulting in

a rise in the rate of NIV success. Dexmedetomidine binds at α_2 receptors rather than GABA receptors, and the cases may be aroused easier with sufficient sedation and present less significant respiratory depression. There were some study limitations in this meta-analysis. Firstly, the number included was limited and all studies were observational. Secondly, most investigations didn't give a specific description of morphine treatment like day-dose and administration route. Lastly, the monitoring period of the study was short.

Also, the outcomes of the MIMO trial (Multicenter, Open-Labeled, Randomized Controlled Trial Comparing midazolam against morphine in Acute Pulmonary Edema) demonstrate that safety was significantly superior in the midazolam group, as SAEs have been found in only ten cases (eighty percent) in comparison with twenty-four cases (forty-three percent) in the morphine group [15].

Some results by Domínguez-Rodríguez *et al.*, [17] were against our study for some reasons, firstly: the treatment wasn't blinded introducing the probability of researcher bias, secondly: the study lasted for four years. Of the 1353 cases with ACPE screened only 111 cases have been involved and randomized throughout this time.

Limitations

Despite the promising results of the current research, the relatively small sample size and the short time of observation (6 hours) have been considered the main limitations. Further research should include more patients with increased statistical power and a broader range of observation time to validate our findings.

CONCLUSION

Dexmedetomidine seemed to be of an advantage over both Morphine and Midazolam regarding outcomes (ICU and hospital stay), however both Morphine and Midazolam revealed advantage over dexmedetomidine concerning dyspnea and sedation scales. Dexmedetomidine is a selective alpha-2 adrenergic agonist, so it has ability to reduce sympathetic activity, provide sedation and analgesia without significant

respiratory depression, and potentially offers neuroprotective and delirium-reducing effects, making it a more favorable option than morphine and midazolam in the management of cardiogenic pulmonary edema.

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Supplementary files:

Tables: TS1, TS2, TS3, TS4, TS5

Figures: FS1, FS2, FS3, FS4, FS5

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Supplementary files:
Table (TS1): On admission Laboratory findings among studied groups (n=84)

Parameter	Morphine Group (n=28)	Midazolam Group (n=28)	Dexmedetomidine Group (n=28)	Test of significance	P value
Na+ Mean± SD Range	133.14 ±6.88 112-143	133.93 ±4.11 129-142	133.54 ±5.50 120-141	F=0.14	0.872
K+ Mean± SD Range	4.11 ±0.54 3.3-5.7	4.16 ±0.48 3.3-5.3	4.25 ±0.50 3.5-5.3	F=0.57	0.569
Cr Mean± SD Range	1.24 ±0.35 0.6-2	1.28 ±0.36 0.7-2	1.21 ±0.45 0.6-2.7	F=0.23	0.792
PH Mean± SD Range	7.49 ±0.04 7.39-7.54	7.50 ±0.02 7.46-7.54	7.48 ±0.06 7.25-7.54	F=0.98	0.381
CO2 Mean± SD Range	29.93 ±2.76 25-35	29.75 ±3.05 21-33	30.11 ±3.54 20-36	F=0.09	0.913
HCO3 Mean± SD Range	19.09 ±1.28 17-22	18.95 ±1.41 16-21	18.93 ±1.91 14-22	F=0.09	0.914

Na: Sodium, K: Potassium, Cr: Creatinine, PH: Potential Hydrogen, CO₂: Carbon Dioxide, HCO₃: Bicarbonate

This table shows a statistically insignificant variance among study groups; according to on admission laboratory findings.

Table (TS2): Follow up Laboratory findings among studied groups (n=84)

Parameter	Morphine Group (n=28)	Midazolam Group (n=28)	Dexmedetomidine Group (n=28)	Test of significance	P value
Na+ Mean± SD Range	135.64 ±3.92 126-141	135.25 ±3.23 128-141	134.82 ±5.14 123-140	F=0.27	0.763
K+ Mean± SD Range	3.71 ±0.41 3.3-5.1	3.70 ±0.41 2.9-4.8	3.85 ±0.47 3.3-5.4	F=1.04	0.358
Cr Mean± SD Range	1.26 ±0.23 0.8-1.7	1.28 ±0.21 0.9-1.8	1.30 ±0.28 0.8-1.9	F=0.18	0.833
PH Mean± SD Range	7.46 ±0.03 7.40-7.50	7.46 ±0.02 7.42-7.50	7.45 ±0.03 7.34-7.50	F=0.35	0.705
CO2 Mean± SD Range	34.14 ±1.56 30-37	33.93 ±1.78 30-37	34.36 ±3.07 26-40	F=0.26	0.774
HCO3 Mean± SD Range	21.94 ±1.77 19.5-26	21.81 ±1.73 18.9-25	21.82 ±1.79 18-25	F=0.04	0.958

This table shows a statistically insignificant variance among study groups; according to follow up laboratory findings.

Table (TS3): On admission and follow up laboratory findings in each studied group (n=84)

Parameter	Morphine Group (n=28)	Midazolam Group (n=28)	Dexmedetomidine Group (n=28)
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	On admission	Follow up	P value	On admission	Follow up	P value	On admission	Follow up	P value
Na+									
Mean± SD	133.14 ±6.88	135.64 ±3.92	0.003*	133.93 ±4.11	135.25 ±3.23	0.025*	133.54 ±5.50	134.82 ±5.14	0.002*
Range	112-143	126-141		129-142	128-141		120-141	123-140	
K+									
Mean± SD	4.11 ±0.54	3.71 ±0.41	<0.001*	4.16 ±0.48	3.70 ±0.41	<0.001*	4.25 ±0.50	3.85 ±0.47	<0.001*
Range	3.3-5.7	3.3-5.1		3.3-5.3	2.9-4.8		3.5-5.3	3.3-5.4	
Cr									
Mean± SD	1.24 ±0.35	1.26 ±0.23	0.621	1.28 ±0.36	1.28 ±0.21	1.000	1.21 ±0.45	1.30 ±0.28	0.056
Range	0.6-2	0.8-1.7		0.7-2	0.9-1.8		0.6-2.7	0.8-1.9	
PH									
Mean± SD	7.49 ±0.04	7.46 ±0.03	<0.001*	7.50 ±0.02	7.46 ±0.02	<0.001*	7.48 ±0.06	7.45 ±0.03	0.027*
Range	7.39-7.54	7.40-7.50		7.46-7.54	7.42-7.50		7.25-7.54	7.34-7.50	
CO2									
Mean± SD	29.93 ±2.76	34.14 ±1.56	<0.001*	29.75 ±3.05	33.93 ±1.78	<0.001*	30.11 ±3.54	34.36 ±3.07	<0.001*
Range	25-35	30-37		21-33	30-37		20-36	26-40	
HCO3									
Mean± SD	19.09 ±1.28	21.94 ±1.77	<0.001*	18.95 ±1.41	21.81 ±1.73	<0.001*	18.93 ±1.91	21.82 ±1.79	<0.001*
Range	17-22	19.5-26		16-21	18.9-25		14-22	18-25	

This table shows statistically significant difference in each study group; regarding admission and follow up laboratory findings, except Cr.

Table (TS4): Outcome among studied groups (n=84)

Parameter	Morphine Group (n=28)	Midazolam Group (n=28)	Dexmedetomidine Group (n=28)	Test of significance	P value	Post Hoc test
ICU stay (Days) Mean± SD Range	7.86 ±1.56 6-11	7.93 ±1.56 5-10	5.50 ±2.17 2-12	H=26.01	<0.001*	P1=0.838 P2<0.001* P3<0.001*
Ward stay (Days) Mean± SD Range	2.46 ±0.99 1-5	2.89 ±0.88 1-4	1.61 ±0.79 1-4	H=24.39	<0.001*	P1=0.090 P2=0.002* P3<0.001*
In-Hospital Mortality Yes No	0 (0) 28 (100)	0 (0) 28 (100)	0 (0) 28 (100)	---	---	----

30-days Mortality	3 (10.7)	2 (7.1)	2 (7.1)	$\chi^2=0.31$	^{MC} 1.000	-----
Yes No	25 (89.3)	26 (92.9)	26 (92.9)			

ICU: Intensive Care Unit

This table shows statistically significant variance among study groups, regarding ICU and Ward stay. This table shows a statistically insignificant variance among study groups; regarding Mechanical Ventilation, In-Hospital Mortality and 30-days Mortality. Regarding hospital stay there was statistically significant decrease in ICU and Ward stay in Dex Group more than Morphine and Midazolam Group.

Table (TS5): Complications among studied groups (n=84)

Parameter	Morphine Group (n=28)	Midazolam Group (n=28)	Dexmedetomidine Group (n=28)	Test of significance	P value
No. of SAE	13	6	10		
Mean± SD	0.39 ±0.63	0.18 ±0.39	0.25 ±0.59	H=2.19	0.335
Range	0-2	0-1	0-2		
Cardiovascular					
Present	9 (32.1)	4 (14.3)	4 (14.3)	$\chi^2=3.69$	0.158
Absent	19 (67.9)	24 (85.7)	24 (85.7)		
Respiratory					
Present	2 (7.1)	1 (3.6)	3 (10.7)	$\chi^2=1.08$	0.867
Absent	26 (92.9)	27 (96.4)	25 (89.3)		
Neurological					
Present	0 (0)	0 (0)	0 (0)	---	---
Absent	28 (100)	28 (100)	28 (100)		
Renal					
Present	0 (0)	0 (0)	0 (0)	---	---
Absent	28 (100)	28 (100)	28 (100)		
Mechanical Ventilation					
Present	2 (7.1)	1 (3.6)	3 (10.7)	$\chi^2=1.08$	^{MC} 0.867
Absent	26 (92.9)	27 (96.4)	25 (89.3)		

H: Kruskal Wallis test

SAE: Serious Adverse Effect

This table shows a statistically insignificant variance among study groups, according to complications.

Score	Description
1	Anxious and agitated or restless, or both
2	Cooperative, orientated, and tranquil
3	Drowsy, but responds to commands
4	Asleep, brisk response to light glabellar tap or loud auditory stimulus
5	Asleep, sluggish response to light glabellar tap or loud auditory stimulus
6	Asleep and unarousable

Figure (FS1): Ramsay score

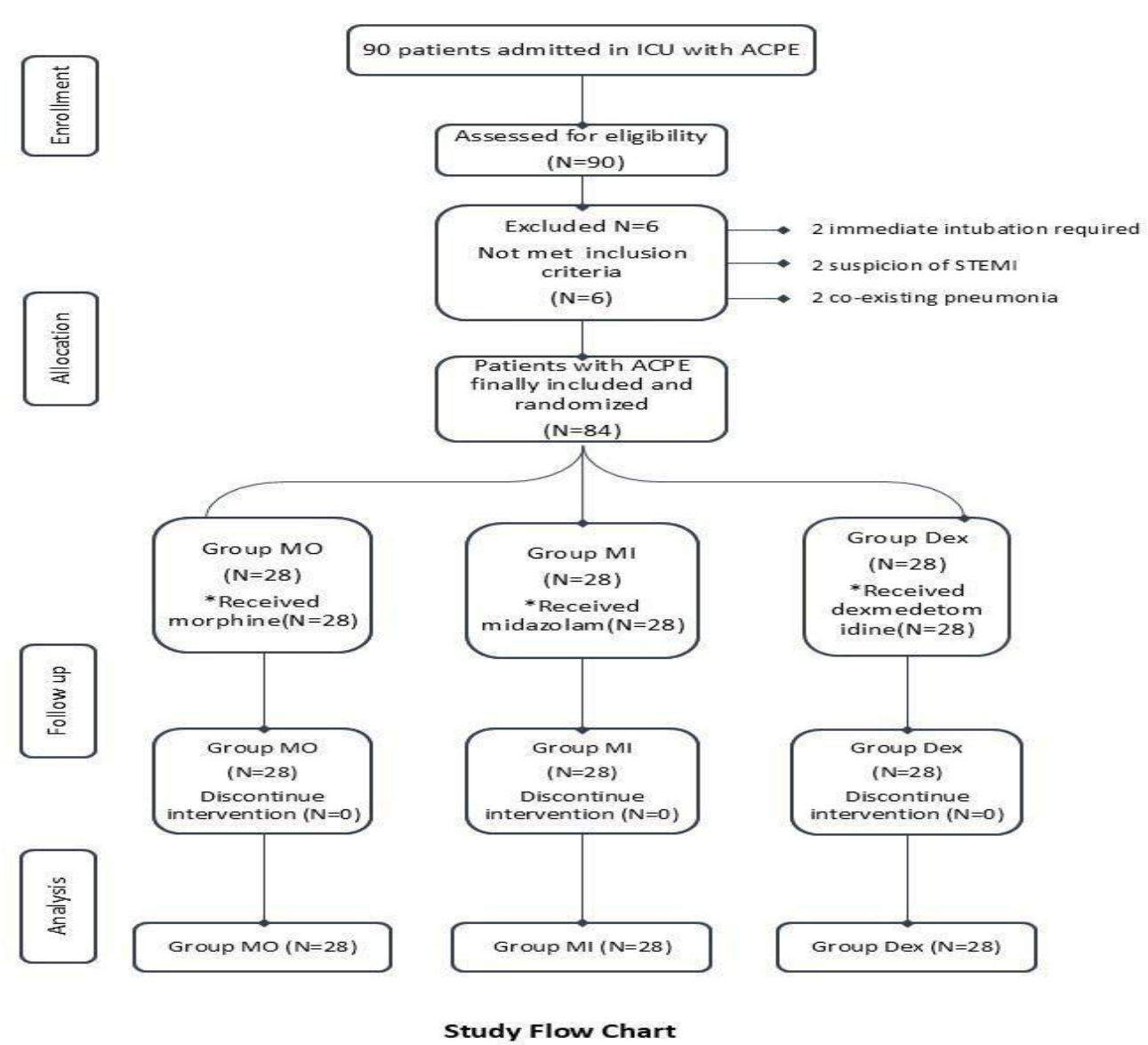


Figure (FS2): Study Flow Chart

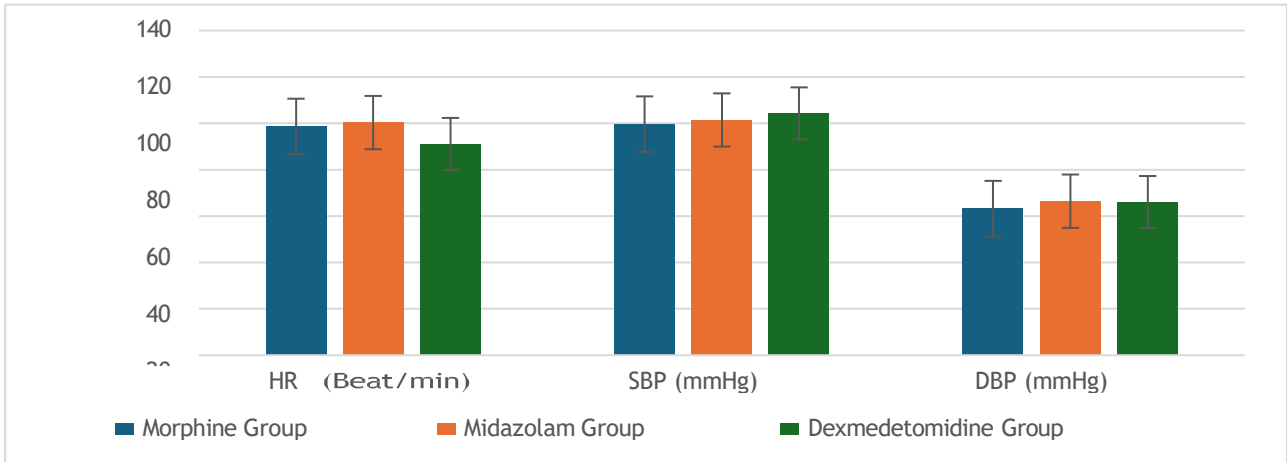


Figure (FS3): Mean of vital signs 6 hours after providing drug among studied groups

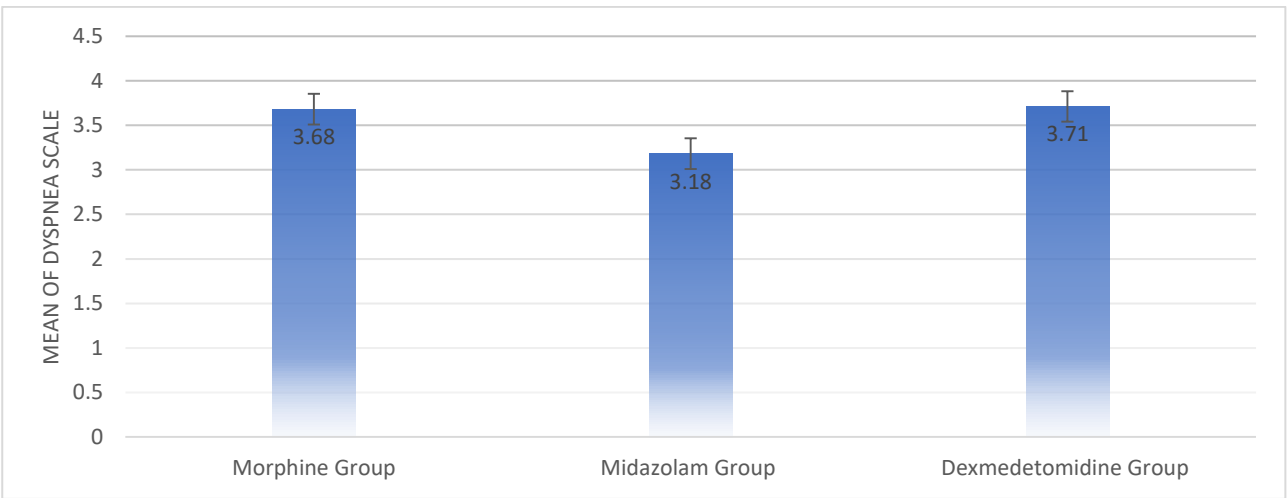


Figure (FS4): Mean of Dyspnea scale among studied group

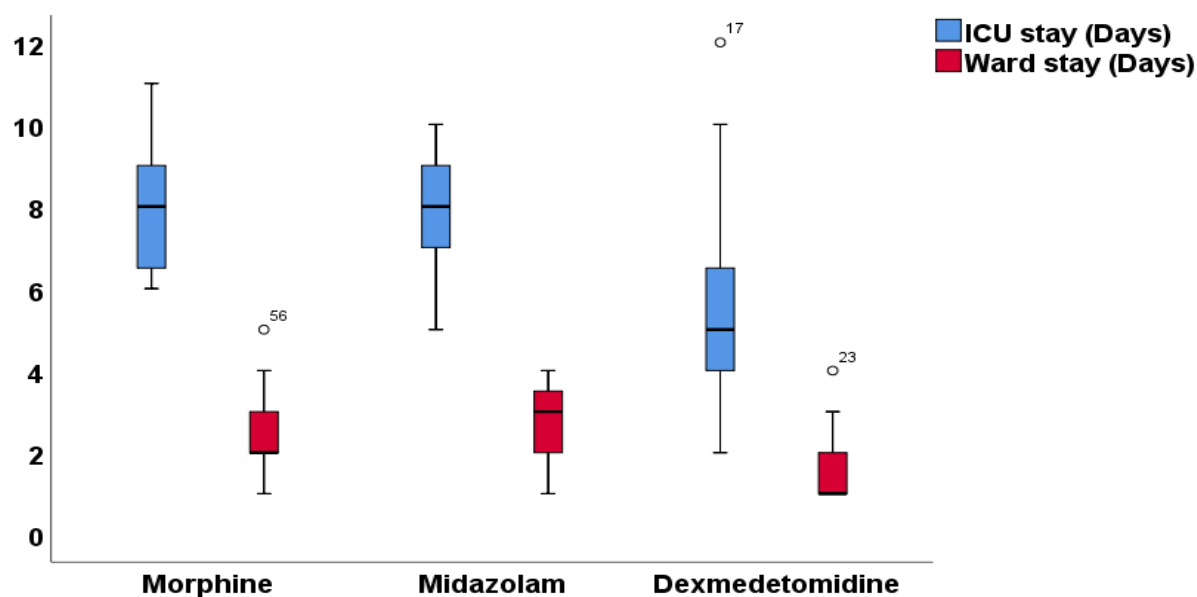


Figure (FS5): Boxplot of length of hospital stay among studied groups

citation

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