Original Research Paper

Volume - 12 | Issue - 04 | April - 2022 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Anaesthesiology

A COMPARATIVE STUDY BETWEEN DEXMEDETOMIDINE AND MIDAZOLAM TO PROVIDE CONSCIOUS SEDATION DURING CENTRAL VENOUS CANNULATION IN INTENSIVE CARE UNIT PATIENTS.

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ABSTRACT **Background:**Conscious sedation is a controlled drug-induced depressed level of consciousness during which patients respond purposefully to verbal commands,either alone or accompanied by light tactile stimulation and retains the ability to maintain a patent airway and spontaneous ventilation is adequate.The study was done to compare the efficacy between Dexmedetomidine and Midazolam to provide Conscious sedation during central venous cannulation in Intensive Care Unit patients.**Materials and Methods:**A comparative,randomized study was carried out on 80 patients with either medical or surgical history who required ICU stay aged 18-65 years of either sex of ASA gradeI-II for central venous cannulation.Patients were randomly divided into two groups (40 each)Group I was given Loading dose of injection Dexmedetomidine 1mcg/kg iv over 10 min followed by an infusion at 0.5mcg/kg/hr .Group II was given Loading dose of 0.05 mg/kg Midazolam over 10min and 0.05mg/kg/hr until Ramsay sedation score reached 3 and hemodynamic variables,numeric pain rating scale,RSS and Modified Aldrete score were compared.Results:Demographic variables were comparable in respect to age, sex,weight and ASA Grade.The significant difference was found in mean MAP between the groups in Group D ($p<0.001$).There was more reduction in MAP in group D. Significant differences were observed at 3 min loading dose and then from 20 min intra op to 1 min post op where fall in pulse rate observed to be more in Group D.The mean time to RSS 3 of group D was 6.53±1.55,the mean time to RSS 3 of group M was 7.98±1.37.The significant difference was found in mean time to RSS3 between the groups ($p<0.001$).The significant difference was found in mean time to achieve modified A.R.S between the groups ($p<0.001$)and was more in group M.No significant difference was found in SPO2 level and N.R.S. between the groups.**Conclusion:**It was concluded that Dexmedetomidine provides better sedation, anxiolysis,hemodynamic stability and faster recovery profile than Midazolam.

KEYWORDS : Conscious sedation,Dexmedetomidine,Midazolam,Central venous cannulation

INTRODUCTION

Central venous cannulation is one of the most commonly performed painful procedures in patients in intensive care unit to provide secure vascular access and rapid administration of fluids[1,2]. Conscious sedation is a controlled drug-induced moderately depressed level of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation and retains the ability to maintain a patent airway, and spontaneous ventilation is adequate, cardiovascular function is usually maintained. Various pharmacological agents have been tried for moderate or conscious sedation like Propofol, Ketamine, benzodiazepine and opioids.

The reason for choosing the study drug is the additional hypnotic, sedative and anxiolytic properties of dexmedetomidine with minimal respiratory depression.

Dexmedetomidine is the S-enantiomer of medetomidine, highly selective α_2- adrenoceptor agonist[3] with α_2:α_1 adreno receptor(1600:1) with sedative,anxiolytic,analgesic,sympatholytic effects and lack of any respiratory depression[4] attributed to the action on Locus Coeruleus,a small nucleus located in dorsal rostral pons.The analgesic effects are mediated by α_2 adrenergic receptors present on superficial dorsal horn in substantia gelatinosa,by inhibiting release of nociceptive transmitter substance P and glutamate. It is known to significantly reduce opioid requirements.Midazolam[5] is an imidazobenzodiazepine with unique properties when compared with other benzodiazepines.The drug produces reliable hypnosis, amnesia, and antianxiety effects and can be used for interventional, diagnostic and therapeutic procedures like central venous cannulation.

Materials and Methods:

This randomised, prospective, Interventional,double blind,non-placebo study titled as A comparative study between Dexmedetomidine and Midazolam for conscious sedation during central venous cannulation in Intensive Care Unit patients was carried out in Anaesthesia Intensive care unit,Swaroop Rani Nehru Hospital Prayagraj over period of one year from June'20 to May'21 after approval from Institutional ethical committee and obtaining written and informed consent from patients.The study was carried out on 80 patients with either medical or surgical history who required ICU stay aged between 18-65 years of either sex of ASA grade I-II.

The study included patients who confirm the following:

INCLUSION CRITERIA :

1) Patients with written informed consent
2) Patient should be alert, awake and oriented.
3) ASA grade I-II patients.
4) Adult patients between 18–65 years of age of either sex.
5) Adults weighing between 45-90kgs.
6) Patient not on ventilator support.
7) Patient should not have received any systemic analgesics in the last 4 hours.

EXCLUSION CRITERIA :

1) Patient refusal.
2) Patient belonging to ASA PS >II.
3) Burns/infection at site of CVP cannulation
4) Uncontrolled cardiovascular disease.
5) History of cerebrovascular disease.
6) Patients with severe hepatic and renal disease.
7) History of bleeding disorders.

Randomization:

Patients were randomized on the basis of a computer generated table of random number using Microsoft Excel,SPSS Version 23.0

GROUP ALLOCATION

Patients were randomly allocated and divided into two groups.

GROUP D	40 PATIENTS	Loading dose of injection Dexmedetomidine 1mcg/kg(100mcg/ml) iv over 10 min followed by an infusion at 0.5mcg/kg/hr
GROUP M	40 PATIENTS	Loading dose of 0.05 mg/kg IV Midazolam over 10min and additional 0.05mg/kg/hr

Both drugs were given till Ramsay Sedation Score reaches 3.

Double blinding:
Double blinding was achieved by the anaesthesiologists–one for preparation of the study drug and administration of the drug and second for data collection. Hence the observer and patient both were unaware of the study.

Statistical Analysis
The results were analyzed using descriptive statistics and making comparisons among various groups.Categorical data were summarized as in proportions and percentages while discrete as mean ±SD.Chi square test is used for testing the association between variables.Unpaired-t test is used to compare means between two groups.A two-sided (α=2) p<0.05 was considered statistically significant.The analysis was done in IBM SPSS version

23.METHODOLOGY
A detailed pre-operative check-up-general examination,systemic examination Complete Blood Count, Viral Markers, Liver function test, Renal function test ,PT INR, X-Ray, Electrocardiogram, Urine Routine and Microscopy,COVID (RT-PCR testing) was carried out.

Patients were randomly allocated and divided into two groups using computer generated random number table (40 patients each):Dexmedetomidine and Midazolam, according to the drug they received for conscious sedation.

Venous access was secured on non-dominant hand of every patient by 18G/20G cannula and Ringer Lactate drip was started. Systemic analgesics were not administered for at least 4hours before the procedure.Vital parameters such as Heart rate, systolic blood pressure (SBP),diastolic blood pressure (DBP),mean arterial pressure and oxygen saturation and electrocardiogram were recorded and readings were taken following the loading dose and every 5 minutes until the completion of the procedure.The procedure was started at the end of loading dose of the study drugs.The patient was placed in the Trendelenburg position (15°-30°) and head tilted 30°to the opposite side.Under full aseptic precautions,Using modified Seldinger technique, aspiration of venous blood confirmed the vein's location and central line was placed.The catheter was then secured, and a sterile dressing was applied. Correct location was confirmed with a chest radiograph.Possible complications such as respiratory depression, allergies, coughing, gagging, nausea and vomiting was recorded.During the procedure if either patient or anaesthesiologist was uncomfortable, the rescue analgesic Injection Paracetamol 10-15mg/kg iv was given.The requirement of rescue analgesic drug was also recorded.During procedure, any of the following complications was observed,recorded and treated accordingly.Oxygen desaturation considered when SpO2 level dropped below 92% for more than 10s and given oxygen at 2-4 litres/minute.A Heart rate under 50 beats/min or 20% decrease from the baseline was labelled as bradycardia, treated with Injection Atropine 0.4-0.6 mg IV, whereas Heart rate over 110 or increase of more than 20% from the baseline level was considered as tachycardia.MAP levels lower than 60 mm Hg or 20% less than the baseline was regarded as hypotension and was managed with Injection Mephentermine 3-5 mg IV.Parameters monitored were blood pressure,pulse rate,SPO2, R.S.S every 3 min from the time of loading dose, every 5 Min during the procedure and 30 min thereafter.Numeric pain rating scale6 for assessing pain.Intra Procedure vitals-B.P, pulse rate, E.C.G, SPO2 every 5 min.Ramsay sedation score every 1 min from the time of loading dose till they attain the Ramsay sedation score of 3 and time taken to attain RSS 3 was noted.Modified Aldrete recovery score7 measured after the end of procedure and time to attain the score of 10 was recorded and shifted to recovery room.

Observations
Table 1: Distribution of Age ,Weight, gender and ASA grading of Cases

Variable	Group M		Group D		Unpaired t test	
	Mean	SD	Mean	SD	t-value	p-value
Age in years	52.6	9.78	56.28	7.1	1.92	0.058
Weight in Kg	62.63	5.72	63.38	7.46	-0.5	0.615
Sex	Group M		Group D		chi sq	p-value
	No.	%	No.	%		
Female	18	45.00%	19	47.50%	0.05	0.823
Male	22	55.00%	21	52.50%		
Total	40	100.00%	40	100.00%		
ASA	Group M		Group D		chi sq	p-value
	No.	%	No.	%		
I	20	50.00%	18	45.00%	0.2	0.654
II	20	50.00%	22	55.00%		

Table 2: Intergroup Comparison of Mean Arterial pressure and pulse rate

Group	Group M		Group D		Unpaired t test	
	Mean	SD	Mean	SD	t-Value	p-value
MAP_Baseline	89.2	4.39	89.72	3.85	-0.57	0.573
MAP_Loading	84.64	3.74	77.08	7.29	5.84	<0.001
MAP_Intra OP	81.93	2.38	74.54	5.15	8.24	<0.001
MAP_Post Op	91.21	2.84	88.58	5.62	2.63	0.01
PR	Group M		Group D		Unpaired t test	
	Mean	SD	Mean	SD	t-value	p-value
0 min (baseline)	81.25	6.65	83.07	6.16	-1.27	0.207
3 min (loading dose)	72.9	5.72	79.88	11.29	-3.49	0.001
6 min(loading dose)	73.85	8.33	74.7	12	-0.37	0.714
10 min (loading dose)	70.88	6.38	72.5	10.91	-0.81	0.419
15 min(intra procedure)	72.18	7.78	69.4	10.97	1.3	0.196
20 min(intra procedure)	71.95	6.46	67.4	10.39	2.35	0.021
25 min(intra procedure)	71.13	6.28	66.73	10.47	2.28	0.025
30 min(intra procedure)	72.4	6.32	66.1	9.85	3.4	0.001
35 min(intra procedure)	72.9	6.82	67.08	8.25	3.44	0.001
40 min(intra procedure)	73.23	7.57	68.63	7.51	2.73	0.008
1 min(post procedure)	81.03	6.27	72.6	6.54	5.88	<0.001
30 min(post procedure)	78.68	4.47	78.58	8.47	0.07	0.948
60 min(post procedure)	79.63	5.35	78.73	6.28	0.69	0.492
90 min(post procedure)	78.03	5.24	79.58	5.3	-1.32	0.192

Table 3: Intergroup Comparison of Time to achieve RSS,SPO2,NRS and ARS

Group	Group M		Group D		Unpaired t test	
	Mean	SD	Mean	SD	t-value	p-value
Variables	5.88	1.62	4.53	1.5	3.87	<0.001
	7.98	1.37	6.53	1.55	4.43	<0.001
SPO2	Group M		Group D		Unpaired t test	
	Mean	SD	Mean	SD	t-value	p-value
0 min (baseline)	99.35	0.48	99.25	0.44	0.97	0.335
3 min (loading dose)	99.3	0.46	99.2	0.56	0.87	0.389
6 min (loading dose)	99.3	0.46	99.18	0.68	0.97	0.338
10 min (loading dose)	99.3	0.46	99.15	0.58	1.28	0.205
15 min(intra procedure)	99.3	0.46	99.28	0.64	0.2	0.842
20 min(intra procedure)	99.3	0.46	99.18	0.59	1.05	0.298
25 min(intra procedure)	99.3	0.46	99.28	0.64	0.2	0.842
30 min(intra procedure)	99.3	0.46	99.28	0.64	0.2	0.842
35 min(intra procedure)	99.3	0.46	99.1	0.67	1.55	0.125
40 min(intra procedure)	99.3	0.46	99.15	0.58	1.28	0.205
1 min(post procedure)	99.3	0.46	99.38	0.49	-0.7	0.484
30 min(post procedure)	99.3	0.46	99.4	0.5	-0.93	0.355
60 min(post procedure)	99.3	0.46	99.38	0.54	-0.67	0.507
90 min(post procedure)	99.3	0.46	99.4	0.5	-0.93	0.355
120 min(post procedure)	99.3	0.46	99.43	0.5	-1.16	0.25
Group	Group M	Group D	Unpaired t test			
	Mean	SD	Mean	SD	t-value	p-value
N.R.S	3.55	1.11	2.8	1.14	2.99	0.004
A.R.S	7.7	1.11	4.7	0.97	-12.87	<0.001

RESULTS:
Demographic variables were comparable in respect to age, sex, weight, and ASA Grade.There was no significant difference in the

baseline systolic blood pressure,mean arterial pressure and SPO_2 between the groups.(Table 1)

The significant difference was found in mean MAP between the groups in Group D ($p<0.001$).There was more reduction in MAP in group **D. (Table 2)**

In our study, significant differences were observed at 3 min loading dose and then from 20 min intra op to 1 min post op where fall in pulse rate observed to be more in Group D.(Table 2)

The mean time to RSS 3 of group D was 6.53±1.55 while the mean time to RSS 3 of group M was 7.98±1.37. The significant difference was found in mean time to RSS 3 between the groups ($p<0.001$).(Table 3)

The mean SPO_2 was above 99% at baseline, at the time of loading dose, at intra op timings and at post procedure timings in both group M and group D. No significant difference was found in SPO_2 level between the groups. (Table 3)

The mean N.R.S of group D was 2.80±1.14 while the mean N.R.S. of group M was 3.55±1.11. No significant difference was found in mean N.R.S. between the groups. (Table 3)

The mean time to achieve modified A.R.S of group D was 4.70±0.97 while the mean time to achieve modified A.R.S. of group M was 7.70±1.11.Significant difference was found in mean time to achieve modified A.R.S. between the groups ($p<0.001$)and was more in group M. (Table 3)

DISCUSSION:

We chose a loading dose of 1 mcg/kg of dexmedetomidine based on previous literature and studies. Reports suggest that on administration of low or moderate doses and slow rates of infusion of dexmedetomidine,α_2 agonist effects are observed but not α_1 effect.The dose regimen used was also similar to study conducted by Sethi P et al[8], Dexmedetomidine versus midazolam for conscious sedation in endoscopic retrograde cholangiopancreatography.Midazolam is most frequently used for agent for conscious sedation.Many favour midazolam because of its fast onset and short duration of action and high amnestic properties.Our findings were similar to study conducted by DevangiA. Parikh et al.,[9] evaluated Dexmedetomidine vs Midazolam-Fentanyl in tympanoplasty,they said that lower heart rate and MAP was found in Dexmedetomidine group in comparison to the Midazolam –Fentanyl group and could be explained by the markedly decreased sympathetic activity.Their findings were similar to other studies where lower heart rate and MAP were observed in the Dexmedetomidine group.The significant difference was found in mean time to RSS 3 between the groups.Similar findings were seen in the study conducted by Suman Shree Ramaswamy and B Parimala[10],on evaluation of two different loading doses of dexmedetomidine with midazolam-fentanyl for sedation in vitreoretinal surgery under peribulbar anaesthesia.Dexmedetomidine was given at a dose of 0.5mcg/kg of loading dose over 10 min.

The time taken to achieve mean A.R.S of group D was 4.70±0.97 while the time taken to achieve mean A.R.S. of group M was 7.70±1.11. The significant difference was found in mean time to achieve A.R.S. of 10 between the groups ($p<0.001$) and was more in group M.Similar results were found by Priyanka Sethi[8] in the study conducted on Dexmedetomidine versus midazolam for conscious sedation in endoscopic retrograde cholangiopancreatography.

CONCLUSION

We conclude that conscious sedation is safe and effective to practise for central venous cannulation and is associated with better patient's co-operation and Dexmedetomidine provides better sedation, anxiolysis,hemodynamic stability and faster recovery profile than Midazolam.

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