

Incidence And Factors Associated With Dexmedetomidine Induced Hypotension And Bradycardia At Moi Teaching And Referral Hospital Intensive Care Unit Eldoret, Kenya

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Abstract- Background: Dexmedetomidine is the preferred drug for light sedation in intensive care units (ICU) where sedation plays an important role in patient comfort. Its advantages include shorter weaning time and earlier extubating from mechanical ventilation without respiratory depression. However, dexmedetomidine has been associated with over 50% incidence of hemodynamic adverse effects (hypotension and bradycardia) that has led to poor clinical outcomes. This limits its widespread use. Factors such as age, comorbidities, concomitant medications, dosage, baseline mean arterial pressure (MAP) and heart rate (HR) have been associated with adverse effects. Despite the high number of reported adverse effects, there is limited data on incidence and associated factors in resource limited settings. Therefore, its burden at Moi Teaching and Referral Hospital (MTRH) remains unknown. Knowledge on incidence and associated factors may inform future practice on safe use of dexmedetomidine at MTRH.

Objective: To determine incidence and clinical factors associated with dexmedetomidine induced adverse effects among patients sedated with dexmedetomidine at MTRH ICU.

Methods: This was a prospective observational study done at MTRH ICU. Hemodynamically stable eligible participants on dexmedetomidine were enrolled through census method between mid-April and mid-October 2022. The dependent variable was incidence of dexmedetomidine induced hemodynamic adverse effects. Data on MAP, HR were collected at selected time points within 24 hours. Independent variables which included factors such as age, gender, comorbidities, concomitant medication, renal, liver functions and drug dosages were obtained from patient records. Cutoff for hypotension was a MAP less than 60mmHg or a drop in MAP of 30% within the first hour, while bradycardia was a HR less than 60bpm or a drop in HR of 30% within first hour of drug administration. Continuous, data was summarized using means, medians and categorical data as frequencies and proportions. Fisher's exact test and Kruskal Wallis test was used to assess for associations between categorical variables and continuous independent variables. The association between the clinical factors and development of

dexmedetomidine induced hemodynamic adverse effects was analyzed using logistic regression model.

Results: A total of 61 participants were recruited and 41% had traumatic brain injury. The mean age was 37 years and males were 63.9%. All participants had baseline HR>60bpm and MAP>60mmHg during drug initiation. Five patients (8.2%) developed hypotension and one (1.6%) developed bradycardia at the first hour. Mean baseline MAP was 90.49mmHg and mean decline was 5.16mmHg at 1hour. Mean baseline HR was 98.75bpm and mean decline was 0.91bpm within the first hour. Majority of patients received drug doses ranging from 0.2 to 0.7mcg/kg/hr for less than 24 hours. Lower baseline MAP<70mmHg was significantly associated with dexmedetomidine hemodynamic adverse effects (OR 2.17[95%CI 1.08-2.97, p<0.01]). However, there was no significant association between gender (0.21), baseline HR (0.88), comorbidities (0.19), concomitant medications (0.15), dose and duration (1), renal (0.28), liver functions (0.17) and occurrence of hemodynamic adverse effects.

Conclusion: This study reported a low incidence of dexmedetomidine induced adverse effects compared to previous studies. Lower baseline MAP<70mmHg was an independent predictor of dexmedetomidine induced hypotension and bradycardia.

Recommendations: Patients with lower baseline MAP<70mmHg and on dexmedetomidine should be monitored more frequently within the first hour.

Index Terms- Dexmedetomidine, Hypotension, Bradycardia, Incidence, Intensive Care Unit

I. INTRODUCTION

Patients in the intensive care unit (ICU) need close attention, including monitoring of organ function, oxygen intake, drug intake for pain, sedation among other services (Temesgen et al., 2021). Sedation is a key aspect in ICU care since it reduces patient discomfort, resolves ventilator asynchrony and also prevents accidental removal of tubes and drains (Ahmed &

Murugan, 2013). Some ICU procedures such as tracheal suctioning is painful and therefore require analgesia and sedation to calm the patient (Temesgen et al., 2021). Due to the above reasons, up to 80% of patients are sedated in the ICU (Neme et al., 2020). Commonly prescribed sedatives in the ICU include benzodiazepines, opioids, alpha 2 adrenergic receptors, propofol and ketamine (Joseph, 2018).

The Society of Critical Care Medicine's (SCCM), 2018 Pain, Agitation/Sedation, Delirium, Immobility and Sleep disruption in adult patients in ICU (PADIS) guideline recommends dexmedetomidine and propofol as the preferred sedative drugs for light sedation among critically ill mechanically ventilated patients in ICU (Devlin et al., 2018). Dexmedetomidine is a highly selective alpha-2 adrenoceptor agonist that produces sedation and hypnosis (Ahmed & Murugan, 2013). It is preferred due to its non-gamma-aminobutyric acid mode of effect that results in dexmedetomidine being the only sedative that has a desirable unique sedative profile that makes patients easily arousable to voice stimulation and are able to cooperate with minimal chance of respiratory depression (Bonfield, Garland, & English, 2021). This unique characteristic has made it much easier for the ICU care team to monitor pain and facilitate the process of weaning and extubation among patients on mechanical ventilation (Gupta, Singh, Sood, & Kathuria, 2015). Dexmedetomidine has an additional mild analgesic effect and also heightens the sensitivity of opioid receptors (Ahn & Kim, 2022). Several high quality studies report a lower incidence of delirium, decreased duration of weaning and extubation, shorter length of ventilator days and length of ICU stay among dexmedetomidine patients compared to other sedatives among patients admitted in the ICU (Bonfield et al., 2021; Mahmoud, 2018). Dexmedetomidine is a fairly new drug when compared to other sedatives in the Kenyan market (Okello, Mung, Adam, & Kabugi, 2018). It was approved for use in the USA by FDA for sedation in ICU in 1999 and as late as 2011 in Europe (Weatherall et al., 2017). Dexmedetomidine was introduced into the Kenyan hospitals in 2014 for use in critical care and surgical anesthesia and later added into the Kenya Essential Medical List in 2019 (Ministry of Health, 2019). The standard recommended dosing of dexmedetomidine is 1mcg/kg over 10 minutes as loading dose and 0.2 to 0.7 mcg/kg/hour for maintenance dosing in ICU for upto 24 hours in patients above 18 years, titrated to clinical effect of light sedation using a Richmond Agitation-Sedation Scale (RASS) (Devlin et al., 2018; Barr, 2013).

Despite having these desirable properties, its widespread use in the intensive care unit (ICU) has been limited by the associated adverse effects of hypotension and bradycardia exceeding 50% (Bonfield et al., 2021; Ice et al., 2016). A multicenter study done in 68 locations across Europe and the U.S.A. comparing effectiveness and safety of dexmedetomidine versus midazolam reported a 42.2% incidence of bradycardia and 56.1 % incidence of hypotension with 4.9% and 9.8% requiring intervention respectively (Riker et al., 2009). These adverse effects have led to increased likelihood of poor clinical outcomes and higher risk of mortality (Gerlach et al., 2016). Dexmedetomidine induced hypotension can also add to the burden of hemodynamic instability which is a common cause of admission in the ICU, leading to increased length of stay

(LOS) in the ICU, which can also lead to other complications such as ventilator associated pneumonia, subsequently increasing cost of care to the patient and hospital (Mathai, Phillips, & Isaac, 2016; Tesema & Lema, 2021). An increased length of stay in the ICU also denies other critically ill patients a chance for admission in resource limited settings (Bahalkeh, Hasan, & Yih, 2022). These adverse effects have limited the uptake and widespread use of dexmedetomidine in ICUs despite its established advantage and desirable characteristics over other sedatives. Other sedative options for light sedation such as benzodiazepines, opioids, ketamine and propofol have also been associated with hemodynamic adverse effects along with respiratory depression in propofol and midazolam, subsequently leading to longer duration of mechanical ventilation due to delayed weaning, extubation and delirium in the ICU (Bonfield et al., 2021).

Driven by the desire to reduce the occurrence of these adverse effects and in turn increase optimization of dexmedetomidine in the ICU, resource rich centres in recent years have focused on determining the predictors of dexmedetomidine induced hypotension and bradycardia among its population to reduce the incidence of these adverse effects. Factors in those settings that have been associated with the adverse effect include the administration of loading dose especially over a short duration of time of less than ten minutes (Devlin et al., 2018). There is also a higher likelihood of developing dexmedetomidine induced bradycardia and hypotension when patients are on concomitant medications that have the ability to lower blood pressure and the heart rate such as opioids, other sedatives, anesthetics and neuromuscular blockers (Pfizer, 2023). Antihypertensives especially diuretics and calcium channel blockers have also been associated with hemodynamic instability among patients on dexmedetomidine (Erdman et al., 2014). Elderly patients above 65 years and those with hepatic impairment and compromised renal functions are also at risk of developing hypotension and bradycardia (Liu et al., 2023; Pfizer, 2023). Comorbidities such as coronary artery disease also play a role in development dexmedetomidine induced adverse effects (Gerlach et al., 2016). Longer duration of drug administration and higher doses of dexmedetomidine may also contribute to dexmedetomidine associated hemodynamic adverse effects (Leung, Wang, & Lee, 2018; Zhao et al., 2018). Hemodynamic factors such as low baseline heart rate and low baseline mean arterial pressure have been associated with dexmedetomidine adverse effects (Gerlach et al., 2016).

The safety of dexmedetomidine has not been well studied in the resource limited settings such as MTRH and only scanty data is available in these settings. This study has been conducted to determine the incidence of dexmedetomidine induced hypotension and bradycardia and the likely factors that contribute to the adverse effects to inform future practice on safe use of dexmedetomidine at MTRH.

II. METHODOLOGY

This study was conducted at MTRH ICU. The hospital is one of the major referral hospitals in Kenya located in Eldoret, Uasin Gishu County, Kenya, with an ICU bed capacity of 21. The study design was a hospital-based prospective observational study.

Mechanically ventilated patients above 18 years on dexmedetomidine who were not on inotropic, vasopressor support or cardiac implantable device were included into the study once they gave an informed consent. MTRH ICU administered dexmedetomidine within a range of 0.2-1.5mcg/kg/hour as continuous IV infusion within a 24 hour period without a loading dose. Routine recording of hemodynamic parameters of heart rate and mean arterial pressure was done on the flow sheet at different time points within 24 hours. This included intervals at baseline, 15 minutes, 30 minutes, 1 hour, 6 hours and 24 hours after dexmedetomidine administration. Patients were then observed for any signs of

III. STUDY FINDINGS

This study was carried out between the months of mid-April and mid-October 2022 at MTRH ICU, Eldoret, Kenya. The study enrolled a total of 61 participants. The mean age was 37.8 years (SD 14.8) with a much higher proportion of males at 63.9% compared to females, 36.1%. Most of the participants (52.5%) had a GCS score of 8 and below while 11.5% had a GCS score of between 12 and 15. There was a total of 47 (77%) participants who were admitted to ICU for mechanical ventilation post-surgery while 14 (23%) were admitted from medical wards. Most of the postoperative admissions were neurosurgical admissions 41(67.2%). Medical admissions indications for mechanical ventilation mostly included respiratory complications 7 (11.5%). 39 (63.9%) participants had no comorbidities while majority of those with comorbidities had hypertension 16 (26.2%) with other comorbidities being each less than 5%. 28 (45.9%) participants were not on any concomitant medications (another sedative, opioid, antihypertensive) at the time of dexmedetomidine initiation. 57 (93.4%) participants had a creatinine clearance of above 30. 40 (65.6%) participants had normal ALT levels, 20 (32.8%) had mild ALT elevation while 1(1.6%) participants had moderate ALT elevation and none had severe ALT elevation. All participants received the same brand of dexmedetomidine. Incidence was any new case of hypotension or bradycardia, as earlier defined, occurring after dexmedetomidine administration. A total of 6 (9.8%) participants experienced dexmedetomidine induced hemodynamic adverse effects within the first hour with majority of adverse effects being hypotension. 5(8.2%) participants had hypotension while 1(1.6%) participant had bradycardia within the first hour. 55 (90.2%) participants did not experience any hemodynamic adverse effect.

All participants had a baseline HR of above 60bpm and baseline MAP of above 60mmHg at baseline before initiation of dexmedetomidine. Majority of the participants had a baseline MAP of 70-100mmHg, while 5 participants had less than 70mmHg and 18 had MAP above 100mmHg. The overall mean baseline MAP for all 61 participants was 90.49mmHg (63mmHg-155mmHg) and the mean decline in MAP over the first hour was 5.16mmHg. Among the 6 participants who experienced hemodynamic adverse events, the mean baseline MAP was 71.2 mmHg (63mmHg- 103mmHg) and the decline in MAP was 9.6mmHg over the first hour. The overall mean baseline HR was 98.75bpm (68bpm-140bpm) while the decline in HR was by 0.91bpm within the first hour. Among the 6 participants, the mean baseline HR was 92.93bpm (80bpm-

hypotension or bradycardia during dexmedetomidine administration. Hypotension was defined as a decrease in systolic BP of more than 30 mmHg or 30% from baseline or a MAP of <60 mmHg. Bradycardia was defined as a HR of less than 60 beats per minute or a greater than 30% reduction from baseline HR.

Approval for the study was obtained from Institutional Research and Ethics Review Committee (IREC), National Commission for Science Technology (NACOSTI) and authorization from MTRH was sought before the recruitment of participants and collection of data for the study.

126bpm) and the highest increase in HR was 6.74bpm over the first hour.

Table 4.8: Incidence, interventions and outcomes of dexmedetomidine associated hypotension and bradycardia

Variable	Total n (%) n-61
Hypotension n (%)	5 (8.2%)
MAP<60mmHg	4 (6.6%)
>30% decrease from baseline	1 (1.6%)
Bradycardia	1 (1.6%)
HR<60bpm	1 (1.6%)
>30% decrease from baseline	0
Intervention for AE	6 (9.8%)
No intervention required	2 (3.3%)
Dexmedetomidine discontinuation	2 (3.3%)
Vasopressor initiation	1 (1.6%)
Fluid bolus administration	1 (1.6%)
Outcomes	
Death attributed to dexmedetomidine	0
Death not attributed to dexmedetomidine	5 (8.2%)
Discharge to wards	56 (91.8%)
Median ICU LOS (patients with AE)	20.5 days (IQR 9.75-22.5)
Median ICU LOS (Patients without AE)	10 days (IQR 6-15.5)

To determine the factors associated with dexmedetomidine induced bradycardia and hypotension, a bivariate analysis using Fisher's Exact Test and Kruskal-Wallis test was done. In this study a P value <0.05 was statistically significant. As shown in the table 4.9, it was observed that age and baseline MAP were statistically significantly associated with dexmedetomidine induced bradycardia and hypotension. Other factors such as gender, baseline heart rate, comorbidities, concomitant medication, kidney function, liver function, renal function, maintenance dose and duration of drug administration were not

statistically associated with dexmedetomidine induced hemodynamic adverse effects.

Table 4.9: Factors associated with dexmedetomidine bradycardia and hypotension

1. Fisher’s Exact Test for Count Data 2. Kruskal-Wallis test

Logistic regression was used which included variables that were significant in table 4.9. Adjusting for age and baseline MAP, a lower baseline MAP <70mmHg was found to be a significant predictor of dexmedetomidine induced hemodynamic adverse effects. While holding all the other factors constant, having a baseline MAP <70mmHg was associated with 2.17 times increase in the odds of developing dexmedetomidine hemodynamic adverse effects.

Table 4.10: Multivariate analysis of factors associated with dexmedetomidine-induced hypotension and bradycardia

Characteristic	AOR	95% CI	P-value
Age in years			
18-39	0.39	0.29-0.47	0.42
40-55	0.89	0.81-0.98	0.2
>55	Ref		
Baseline MAP			
<70	2.17	1.08-2.97	<0.01*
>100	1.25	1.13-1.32	0.19
70-100	Ref		

Variable	Pts with Hemodynamic adverse effect (N=6)	Pts without hemodynamic adverse effect (N=55)	P value
	Frequency (%)	Frequency (%)	
Gender			
Female	4 (18%)	18 (82%)	0.21 ¹
Male	2 (5%)	37 (95%)	
Age			
18-39	1 (3%)	32 (97%)	0.03 ¹
40-55 years	3 (15%)	17(85%)	
≥55 years	2 (25%)	6 (75%)	
GCS Score			
8 and below	4 (12.5%)	28 (87.5%)	0.16 ¹
9-12	1 (4.6%)	21 (95.4%)	
13-15	1 (16.7%)	5 (83.3%)	
ICU admission			
Medical	1 (7%)	13 (93%)	0.713 ¹
Surgical	5 (11%)	42 (89%)	
Comorbidities			
No	3 (8%)	36 (92%)	0.19 ¹
Yes	3 (14%)	19 (86%)	
Concomitant			
None	3 (10.7%)	25 (89.3%)	0.15 ¹
Antihypertensive	2 (12.5%)	14 (87.5%)	
Opioid	0	12 (100%)	
Combination	1 (25%)	4 (75%)	
Kidney function			
Crcl >30	5 (9%)	52 (91%)	0.28 ¹
Crcl ≤30	1 (25%)	3 (75%)	
Liver function			
Normal ALT	5 (13%)	35 (87%)	0.17 ¹
Mild elev	1 (5%)	19 (95%)	
Mod elev	0	1 (100%)	
Severe elev	0	0	
Maintenance dose			
≤0.7 µg/kg/hr	6 (10%)	52 (90%)	1 ¹
>0.7 µg/kg/hr	0	3 (100%)	
Duration of sedation			
≤24hrs	6 (12%)	48 (88%)	1 ¹
>24hrs	0	7 (100%)	
Baseline HR			
Count	6	55	0.88 ²
Mean	101.6	98.5	
Range	(80-126)	(68-140)	
Baseline MAP			
<70	4 (80%)	1(20%)	<0.001 ¹
70-100	1 (2.6%)	37 (97.4%)	
>100	1 (5.6%)	17 (94.4%)	

IV. CONCLUSION

This study reported a low incidence of dexmedetomidine induced hemodynamic adverse effects compared to previous studies. A lower baseline MAP < 70mmHg was an independent predictor of dexmedetomidine induced hypotension and bradycardia. Patients with lower MAP < 70mmHg and on dexmedetomidine should be monitored more frequently for dexmedetomidine induced hemodynamic adverse effects within the first hour.

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