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Original Article

Dexmedetomidine as an Adjunct to Anti-Hypertensive Medication in Hemodynamic Management of Post-Operative Young Patients with Pre-Eclampsia

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ABSTRACT

Objective: To compare hemodynamic stability and patient outcomes when using dexmedetomidine as an adjunct to anti-hypertensive medication in post-operative young patients with pre-eclampsia

Study Design: Quasi-experimental study

Place and Duration of Study: Department of Anesthesia, Combined Military Hospital Bannu, Pakistan from 15 Jan - 15 Dec 2023.

Methodology: A total of 180 patients were recruited for this quasi-experimental study. Patients were divided into Group-D (n=80) to receive Dexmedetomidine along with standard anti-hypertensive therapy, which included intravenous Labetalol, and Group-S (n=80) to receive standard anti-hypertensive therapy with intravenous Labetalol alone. Primary variables studied were hemodynamic profile in all patients, including heart rate and blood pressure checked at 1,3,6,12,18, and 24 hours. Secondary variables studied were sedation levels, mean total dose of analgesia required for post-operative pain in 24 hours, and the incidence of adverse effects including bradycardia, hypotension, nausea/vomiting and headache.

Results: Mean arterial pressure (MAP) after 01 hour of therapy between Group-D and Group-S was 98.64±1.63 mmHg versus 100.55±4.75 mmHg (p=0.001), after 03 hours of therapy was 85.56±1.27 mmHg versus 89.13±2.29 mmHg (p<0.001), after 06 hours of therapy was 77.56±1.36 versus 89.35±2.90 mmHg (p<0.001), after 12 hours of therapy was 74.33±1.38 mmHg versus 82.94±4.26 mmHg (p<0.001), after 18 hours of therapy was 70.46±0.82 mmHg versus 78.61±0.60 mmHg (p<0.001) and after 24 hours of therapy was 67.99±1.08 mmHg versus 78.64±0.57 mmHg (p <0.001).

Conclusion: Addition of Dexmedetomidine to standard anti-hypertensive therapy results in a better hemodynamic profile, better patient comfort, less requirement for analgesia with a tolerable adverse effects profile.

Keywords: Adjunct anti-hypertensive, Dexmedetomidine, Pre-eclampsia

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INTRODUCTION

Pre-eclampsia is defined as arterial hypertension diagnosed after the 20th week of gestation in obstetric patients with evidence of proteinuria.[1] The definition has eliminated rigid criteria for diagnosing pre-eclampsia. In the absence of proteinuria, the presence of symptoms such as headache, visual disturbances, abdominal discomfort, abnormal renal and liver function, and involvement of the pulmonary and nervous systems can indicate the diagnosis in suspected patients.[2] The overall incidence for pre-eclampsia is varied but a conscious estimate shows that it occurs in 3-5% of all pregnancies.[3] It can occur after the 20th week and continue in the immediate post-partum period as well. It is associated with considerable morbidity as well as mortality both for the mother and the baby, and requires early diagnosis, vigilant monitoring, and tailored treatment to prevent turning into eclampsia, a catastrophic complication associated with generalized tonic clonic seizures associated with high maternal and fetal mortality. Studies have shown that while pre-eclampsia is complicated with increasing maternal age, the incidence of pre-eclampsia is twice as high in young females.[4]

The treatment options have been studied in detail, including the Magee *et al*.[5] meta-analysis and the CHIPS study[6], concluding that early initiation of anti-hypertensive therapy, either oral or intravenous, results in lower pre-maturity rates, episodes of thrombocytopenia, and improves fetal weight. Most of these patients require intravenous therapy after the delivery of the baby. First-line treatment options include intravenous Labetalol, Hydralazine, Magnesium Sulphate, Nifedipine, to name a few.[7] While these therapies are effective, sometimes patients require more than one drug for control of blood

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pressure in severe cases. In patients where there is a contraindication to use any of the first and second line drugs mentioned, alternate therapies are considered for control of blood pressure in the post-operative period.

Dexmedetomidine is an alpha agonist and possesses sedative, anxiolytic, hypnotic and sympatholytic properties.[8] Studies have reported its beneficial effects in blunting hemodynamic responses in patients, and we aim to see its role as an adjunct to hypertensive medication post-operatively in young patients with pre-eclampsia.

METHODOLOGY

This quasi-experimental study was carried out at the Department of Anesthesiology, Combined Military Hospital Bannu from 15 January 2023 to 15 December 2023 after approval from the ethical review board (vide letter no. 03/2023).Minimum sample size to be taken was calculated using the WHO calculator keeping the confidence interval at 95%, power of test at 80% with the anticipated post-operative mean arterial pressure (MAP) values being 93.16±5.68 mmHg in the Dexmedetomidine infusion group versus 108.70±4.69 mmHg in the standard anti-hypertensive therapy group.[9] Comparing the mean difference of MAP values between the two groups for minimum sample size using the WHO calculator calculated a sample size of 66 for each group. We included 80 patients in each group making the final study sample of 160 patients using non-probability consecutive sampling.

Inclusion Criteria: ASA-III obstetric patients aged 18-25 years diagnosed with pre-eclampsia shifted to the high dependency unit (HDU) after a high risk caesarian section under anesthesia with a postoperative blood pressure above 150/100 mmHg despite pre and per-operative anti-hypertensive therapy were included in the study.

Exclusion Criteria: Patients with eclamptic fits in the pre-operative period, severe thrombocytopenia and acute kidney injury evidenced by blood panels, patients with decreased urine output <0.5 ml/kg/hr, those requiring ventilatory support after surgery, debilitating cardiac or respiratory disease, allergic to Labetalol or Dexmedetomidine and non-consenting patients were excluded.

Patients were randomly divided into Group-D (n=80) to receive Dexmedetomidine along with standard anti-hypertensive therapy which included intravenous Labetalol and Group-S (n=80) to receive standard anti-hypertensive therapy with intravenous Labetalol alone (Figure). All the patients in the study were counselled pre-operatively about inclusion in the study protocol without the patients knowing the group in which they were placed and possible complications of the treatment regimens.

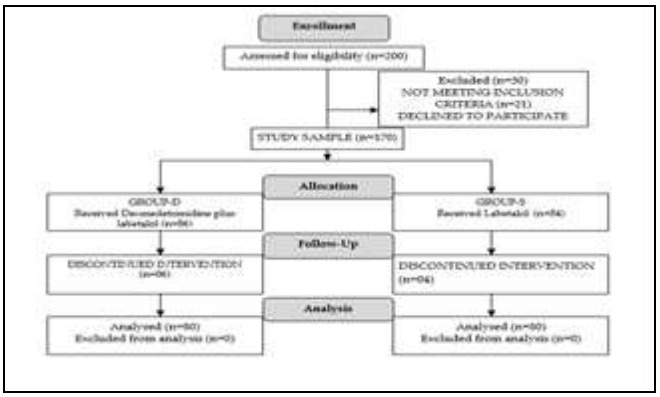

Figure: Phases of the Study Protocol

Patients in both groups were received in the HDU after being shifted from the operating room recovery. Initial heart rate and blood pressure reading was recorded in all patients while lying on bed and the same was repeated after 10 minutes. All patients of both groups received IV Magnesium Sulphate as prophylaxis for eclampsia at a bolus dose of 4g given over 20 minutes in the HDU. It was followed by an infusion in Intravenous Labetalol in Group-S at a rate of 5 mg/hr titrated through an infusion pump. Patients in Group-D received Intravenous Labetalol at the same infusion dose as Group-S with added Intravenous Dexmedetomidine infusion started at a rate of 0.5 mcg/kg/hr. The infusions were continued for a minimum for 24 hours in both groups and doses were adjusted to maintain a target blood pressure in all patients of less than 130/90 mmHg. Bradycardia and hypotension (Heart rate < 60 bpm and MAP < 50 mmHg).[10] were indications to stop infusions. The infusion was continued if values exceeded 150/100 mmHg, 15 minutes apart in one hour. If the blood pressure remained above 150/100 mmHg after 1 hour of infusions, the rates were increased to a maximum of IV Labetalol 10 mg/hr and IV Dexmedetomidine at 1.0 mcg/kg/hr. If a third drug was needed to control blood pressure or fits occurred in any patient, they were excluded from the study protocol. Bradycardia was treated with Intravenous Atropine if needed and hypotension was treated with Intravenous Phenylephrine titrated to affect.[11] Pain was treated in

the post-operative period with IV Paracetamol 1 g stat when scores on the NRS12 score were above 40 in all patients and total dose was recorded in 24 hours.

Primary variables studied were hemodynamic profile in all patients including heart rate and blood pressure checked at 1,3,6,12,18, and 24 hours. Secondary variables studied were sedation levels using the Ramsay sedation score, mean total dose of analgesia required for post-operative pain in 24 hours, and the incidence of adverse effects including bradycardia, hypotension, nausea/vomiting and headache.

Demographic data were statistically described in terms of mean and SD, frequencies, and percentages when appropriate. T-test was used to compare statistically significant means between both groups. Median values were compared using the Mann Whitney-U test. Chi-square test was used for secondary variables. The *p* value of <0.05 was considered statistically significant. All statistical calculations were performed using Statistical Package for Social Sciences 26.0.

RESULTS

A total of 170 patients were included in the initial study sample after meeting the inclusion criteria and consent for inclusion. 06 patients in Group D and 04 patients in Group S were excluded from the study due to episodes of fits and requiring ventilatory support. The final sample analyzed consisted of 160 patients divided into Group-D (n=80) and Group-S (n=80). Mean age of patients in Group-D was 22.39±2.93 years versus 22.44±2.92 years in Group-S (*p*=0.914). Mean weight was 73.56±3.88 kg in Group-D versus 73.70±3.88 kg in Group-S (*p*=0.823). Mean duration of surgery was 70.89±4.05 minutes versus 71.20±4.28 minutes between both groups (*p*=0.636). Gravida status of patients between both groups revealed that 12(15%) patients in Group-D versus 15(18.8%) in Group-S were primigravida and 68(85%) patients in Group-D versus 65(81.3%) patients in Group-S were multigravida (Table-I).

Table-I : Demographic Characteristics of Groups (n=160)

Variables	Group-D (n=80)	Group-S (n=80)	*p*-value
Mean Age (years)	22.39±2.93	22.44±2.92	0.914
Mean Weight (kg)	73.56±3.88	73.70±3.88	0.823
Mean Duration of Surgery (min)	70.89±4.05	71.20±4.28	0.636
Gravidity			
Primi gravida	12(15%)	15(18.8%)	-
Multi gravida	68(85%)	65(81.3%)	-

Study of primary variables revealed that mean arterial pressure (MAP) after 01 hr of therapy between Group-D and Group-S was 98.64±1.63 mmHg versus 100.55±4.75 mmHg (*p*=0.001), after 03 hrs of therapy was 85.56±1.27 mmHg versus 89.13±2.29 mmHg (*p*<0.001), after 06 hours of therapy was 77.56±1.36 versus 89.35±2.90 mmHg (*p*<0.001), after 12 hours of therapy was 74.33±1.38 mmHg versus 82.94±4.26 mmHg (*p*<0.001), after 18 hours of therapy was 70.46±0.82 mmHg versus 78.61±0.60 mmHg (*p*<0.001) and after 24 hours of therapy was 67.99±1.08 mmHg versus 78.64±0.57 mmHg (<0.001) (Table-II).

Heart rate between Group-D and Group-S after 01 hr of therapy was 107.49±3.29 bpm versus 114.52±1.76 bpm (<0.001), after 03 hrs of therapy was 88.18±1.69 mmHg versus 95.89±3.62 mmHg (*p*<0.001), after 06 hours of therapy was 80.76±3.42 bpm versus 91.15±3.05 bpm (*p*<0.001), after 12 hours of therapy was 75.90±1.13 bpm versus 87.74±1.38 bpm (*p*<0.001), after 18 hours of therapy was 75.43±0.93 bpm versus 87.16±0.97 bpm (*p*<0.001) and after 24 hours of therapy was 71.88±2.31 bpm versus 78.51±1.56 bpm (*p*<0.001) (Table-II).

Table-II: Comparison of Primary Variables among Groups (n=160)

Variables	Group-D (n=80)	Group-S (n=80)	*p*-value
Mean Arterial Pressure (mm Hg)			
01 hour of therapy	98.64±1.63	100.55±4.75	0.001
03 hours of therapy	85.56±1.27	89.13±2.29	<0.001
06 hours of therapy	77.56±1.36	89.35±2.90	<0.001
12 hours of therapy	74.33±1.38	82.94±4.26	<0.001
18 hours of therapy	70.46±0.82	78.61±0.60	<0.001
24 hours of therapy	67.99±1.08	78.64±0.57	<0.001
Heart Rate (bpm)			
01 hour of therapy	107.49±3.29	114.52±1.76	<0.001
03 hours of therapy	88.18±1.69	95.89±3.62	<0.001
06 hours of therapy	80.76±3.42	91.15±3.06	<0.001
12 hours of therapy	75.90±1.13	87.74±1.38	<0.001
18 hours of therapy	75.43±0.93	87.16±0.97	<0.001
24 hours of therapy	71.88±2.31	78.51±1.56	<0.001

Sedation scores using the Ramsay agitation sedation score between both groups after 3 hours were -1.00 (1.00) in Group-D versus 1.00 (1.00) in Group-S (p<0.001), assessed after 06 hrs were -1.00 (1.00) versus 0.00 (1.00) between both groups (p<0.001), and after 12 hrs were -2.00 (1.00) versus 0.00 (1.00) between Group-D and Group-S respectively. Mean total dose of analgesia required in first 24 hours after pain scores assessment was 1.73±0.44 grams versus 2.71±0.45 grams between both groups (p<0.001) (Table-III).

Adverse effects profile showed bradycardia was seen in 12(15%) patients in Group-D versus 03(3.8%) patients in Group-S (p=0.015), hypotension in 11(13.8%) versus 05(6.3%) patients (p=0.114), nausea/vomiting in 11(13.8%) versus 05(6.3%) patients (p=0.114) and headache was noted in 08(10%) versus 03(3.8%) patients (p=0.118) (Table-III).

Table-III: Comparison of Secondary Variables Among Both Groups (n=160)

Variable	Group-D (n=80)	Group S (n=80)	*p*-value
Median Ramsay Sedation Scores			
3 hours	-1.00 (1.00)	1.00 (1.00)	<0.001
6 hours	-1.00 (1.00)	0.00 (1.00)	<0.001
12 hours	-2.00 (1.00)	0.00 (1.00)	<0.001
Mean Total Dose of Analgesia Required for Pain (gm/24 hr)	1.73±0.44	2.71±0.45	<0.001
Adverse effects			
Bradycardia	12 (15%)	03 (3.8%)	0.015
Hypotension	11 (13.8%)	05 (6.3%)	0.114
Nausea/Vomiting	11 (13.8%)	05 (6.3%)	0.114
Headache	08 (10%)	03 (3.8%)	0.118

DISCUSSION

This study demonstrated that addition of Dexmedetomidine to standard anti-hypertensive therapy with Intravenous Labetalol results in a better hemodynamic profile, better patient comfort, less requirement for analgesia with a tolerable adverse effect profile. Dexmedetomidine is an alpha-2 agonist with a diverse set of effects including analgesic, hypnotic, sedative, anxiolytic and sympatholytic. Its use in the field of anesthesia was initially employed in ICU sedation where it provided mild sedation, enough for patient comfort but also allowing neurological assessment when needed.[13] This was in stark contrast to Barbiturates and Benzodiazepines, and the drug achieved widespread acceptance in the field of critical care and anesthesia. The main concerns with the drug after studies done was the incidence of hypotension and bradycardia usually seen after the first six hours of therapy.[10] It was also observed that the incidence was higher when used as a single drug at maximum dose. The mechanism by which Dexmedetomidine exerts its effects are multiple including activation of receptors in the brain (central and post-synaptic) and spinal cord inhibiting neuronal firing causing hypotension, bradycardia, sedation and analgesia.[14] While studies have been done to explore its role in blunting hemodynamic responses during anesthesia, as an adjunct to ICU sedation and its use for prolonging the action of neuraxial anesthesia, its role as an anti-hypertensive has not been documented in detail in high risk groups including young obstetric patients with pre-eclampsia where the incidence is twice as high than patients with advanced age.

Our study to our knowledge is the first of its kind in our demographic setup in using Dexmedetomidine as an adjunct to anti-hypertensive medication. Demographic factors revealed that among the young patients included, more than 85% of cases were multigravida. Studies done internationally have shown a strong association between multiple pregnancies and onset of pre-eclampsia in subsequent pregnancies.[15] The hemodynamic parameters studied show that there was a consistently better fall in both the mean arterial pressure and heart rate, with the Dexmedetomidine group showing a more conducive profile than the Labetalol group. We also found that in Group-D, the values during the first one hour were statistically significant for mean arterial pressure but not clinically significant. This is attributed to the effect of Dexmedetomidine with an initial hypertension followed by hypotension and bradycardia.[16]

We also found that the Ramsay Agitation Sedation score was in the mild sedation range in the Dexmedetomidine compared to fully awake or slightly restless patients in Group-S documented in international studies as well.[17] The patients in Group-D with the dose of Dexmedetomidine infusion resulted in added relaxation and anxiolysis with the patients easy arousable and more relaxed than those in the Labetalol group. We believe that this resulted in an earlier fall in the heart rate and blood pressure with the added advantage of patient comfort. The use of pain killers (Paracetamol) was considerably less in the Dexmedetomidine group attributed to this sedative and analgesic profile which provides a clear advantage in reducing the use of pain killer in the immediate post-operative period. A study done by

Liaquat *et al.*,[8] and Bao *et al*.[18] have demonstrated its neuroprotective effects in reducing the chance of delirium, stroke and fits and this new avenue needs to be investigated further in eclampsia patients for potential benefit.

The adverse effect profile showed that the significant issue of bradycardia was higher in the Dexmedetomidine group but further analysis of our study that in the infusion range that was used, the values of heart rate did not require cessation of therapy in any patient and Atropine was required in only two patients in Group-D.

RECOMMENDATIONS

The study recommends the use of dexmedetomidine as a suitable adjunct to standard anti-hypertensive therapy to treat post-operative pre-eclampsia.

CONCLUSION

We conclude that adding Dexmedetomidine to standard anti-hypertensive therapy results in a better hemodynamic profile, better patient comfort, less requirement for analgesia with a tolerable adverse effects profile.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MFN & IUH: Conception, study design, drafting the manuscript, approval of the final version to be published.

MA & FAJ: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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