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Research article

Intubation stress responses: Pre-anesthetic dexmedetomidine versus fentanyl in pre-eclamptic patients undergoing caesarean delivery: A prospective double blind randomized study

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ABSTRACT

Background: The cardiovascular response to laryngoscopy and endotracheal intubation occurs due to sympathetic stimulation. This effect is exaggerated in pre-eclamptic patients. The aim of this study is to evaluate the effects of dexmedetomidine given over 10 min and fentanyl 3 min before induction of anesthesia on the blood pressure and heart rate changes during laryngoscopy and tracheal intubation in sever pre-eclamptic patients, and their effect on the neonatal outcome.

Methods: 88 sever pre-eclamptic undergoing elective caesarean section under general Anesthesia, were randomly assigned to receive either Dexmedetomidine (0.5 μg kg^{-1}) over 10 min or fentanyl (1 μg kg^{-1}) 3 min before induction of anesthesia. Systolic, diastolic and mean arterial pressure and heart rate were recorded just before initiating laryngoscopy and tracheal intubation and at 1 min intervals up to 5 min thereafter. The neonatal outcome was assessed by using Apgar score at 1, 5 and 10 min after delivery and analysis of umbilical artery blood gases.

Results: Mean arterial pressure was significantly decreased after administration of the Dexmedetomidine from (112.89 ± 5.14) to (101.56 ± 3.89) mmHg, after endotracheal intubation (108.14 ± 3.21), the measured hemodynamic variables remained significantly lower than the baseline values ($P < 0.05$). In fentanyl group, the mean arterial pressure (118.07 ± 4.05) significantly increased after endotracheal intubation as compared to the baseline values (111.75 ± 5.15) ($P < 0.05$). Apgar score at 1, 5 and 10 min and umbilical artery blood gases analysis after delivery were statistically insignificant between both groups.

Conclusions: Dexmedetomidine given over 10 min before induction of general anesthesia significantly reduced the measured hemodynamic variables compared to baseline values. Dexmedetomidine successfully attenuated the intubation stress response and provided a significant hemodynamic stability more than fentanyl which given 3 min before the induction of anesthesia in sever pre-eclamptic patients. Neither drug was associated with any harmful neonatal outcome.

Pan African Clinical Trials Registry (PACTR201508001198128).

1. Introduction

Pre-eclampsia is one of the most common causes of high risk pregnancy that leads to increased maternal and fetal morbidity and mortality [1]. A section of pre-eclamptic patients do caesarean delivery under general anesthesia for several reasons; Some of them refuse regional anesthesia, others have borderline or low platelet count, and fetal heart rate in many cases was not reassuring.

The cardiovascular response to laryngoscopy and endotracheal intubation occurs due to sympathetic stimulation that results in increased plasma concentration of catecholamines [2,3]. This cardiovascular response may lead to myocardial ischemia and acute heart failure [4]. Also, it may affect the fetus due to increased catecholamine concentrations and decreased the utero-placental blood flow [5–7]. This effect is exaggerated in pre-eclamptic patients [8,9].

The prevention or attenuation of cardiovascular response to airway instrumentation is an important issue. The cardiovascular

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response can be attenuated by several techniques i.e. premedication with beta blocker [10], nitroglycerine [11] and calcium channel blockers [12].

Dexmedetomidine is highly selective α2 adrenergic agonist [13], that results in decrease the sympathetic outflow and decreased the blood level of catecholamines especially epinephrine [14,15]. It is more effective and faster acting than clonidine [16].

We hypothesized that the sympatholytic effects of dexmedetomidine may blunt the hemodynamic exaggerated response to tracheal intubation as a safe and effective substitute for fentanyl.

The present study was designed to evaluate the effects of dexmedetomidine given over 10 min and fentanyl 3 min before induction of anesthesia on the changes in blood pressure and heart rate (HR) observed during laryngoscopy and tracheal intubation in in sever pre-eclamptic patients, as a primary goal and their effect on the neonatal outcome as a secondary goal.

2. Methods

After obtaining approval of the Research Ethics committee (Faculty of Medicine, Tanta University, Egypt; code number: 30139/03/31), registration in the Pan African Clinical Trials Registry (PACTR201508001198128). A written informed consent was taken from the patient and her husband. A prospective double blinded randomized study was carried out between August 2015 and March 2016. Women aged $\geqslant$18 years with sever pre-eclampsia that had contraindications or refused neuraxial block, scheduled for caesarean deliveries were included in the study.

Pre-eclampsia was considered as severe in the presence of the following

- The systolic arterial pressure (SAP) exceeds 160 mmHg, or the diastolic arterial pressure (DAP) exceeds 110 mmHg, or both.
- If the patient has symptoms of imminent eclampsia (severe headache, visual disturbance, epigastric pain, vomiting, or hyper-reflexia).
- Proteinuria 3+ or worse.

The exclusion criteria were: morbid obesity, history of diabetes mellitus, cardiac diseases, renal and hepatic dysfunction, presence of known fetal anomalies and history of allergy to the studied drug.

Randomization was performed using a computer-generated randomization sequence into two groups by using sealed opaque envelope. The envelope was opened, the included number was read and group assignments as 1: 1 group ratio was made by an anaesthesiology resident who had no subsequent role in the study.

- Dexmedetomidine group (Group Dex): received dexmedetomidine at dose of 0.5 μg kg^{-1}. Dexmedetomidine was prepared in 50 ml normal saline.
- Fentanyl group (Group Fent): received fentanyl at dose of 1 μg kg^{-1}. Fentanyl was prepared in 10 ml normal saline.

Patients received care treatment for pre-eclampsia according to the standard protocol of the Obstetrics & Gynaecology Department of Tanta University Hospitals, including: Antihypertensive medication (Oral α-methyl dopa) and magnesium sulphate (4 g I V as loading dose followed by 1 g h^{-1} infusion) as seizure prophylaxis. Hydralazine 2.5–5 mg was given at 20 min intervals for SAP >160 mmHg or DAP >110 mmHg.

All patients received intravenous ranitidine 50 mg one hour before induction of general anesthesia.

On arrival to the operating theatre, standard monitoring was applied; non-invasive arterial blood pressure, electrocardiography, end-tidal CO_2 and peripheral oxygen saturation. All patients were placed supine with left lateral tilt. Peripheral intravenous line was secured and arterial cannula 20 G was inserted in the radial artery under local anesthesia with lidocaine 2% for invasive monitoring of blood pressure.

Dexmedetomidine group received dexmedetomidine (0.5 μg kg^{-1}) in 50 ml normal saline infusion over 10 min and 10 ml normal saline 3 min before induction.

Fentanyl group received 50 ml normal saline infusion over 10 min and fentanyl 1 μg kg^{-1} diluted in 10 ml of normal saline 3 min before induction.

The study solutions were prepared by anaesthesiology resident that had no further role in the study. The administered medications, patients monitoring, laryngoscopy and intubation were performed by an anesthesia team who was blinded to the given drug. All staff in the operating room was unaware of patient allocation.

After adequate pre-oxygenation for 3–5 min, anesthesia was induced by rapid-sequence induction with i.v. propofol 2 mg kg^{-1} and succinylcholine 1.5 mg kg^{-1}. If there was more than one attempt for endotracheal intubation or endotracheal intubation attempt took >40 s, the patient was excluded from the study. Anesthesia was maintained with isoflurane 0.75% in gas mixture of oxygen: air 40:60 using a circle circuit with a fresh gas flow of 6 L/min till the time of delivery. After delivery, the fresh gas flow was reduced to 4 L/min.

Muscle relaxation was maintained with atracurium 0.3 mg kg^{-1} within few minutes of succinylcholine administration, and the lungs were mechanically ventilated to maintain the end-tidal CO_2 30–35 mmHg.

Immediately after delivery of the fetus, IV oxytocin (40 IU in 1000 ml normal saline solution) infusion was given. Intraoperative hypotension (SAP less than 100 mmHg) was treated by increasing i.v. crystalloid infusion (15 ml/kg crystalloids), followed by ephedrine 8 mg bolus if SAP decreased below 90 mmHg. Bradycardia was defined as HR $\leqslant$ 50 beat/min and was treated with i.v. bolus of atropine 0.5 mg as required.

At end of surgery, isoflurane was discontinued and neuromuscular block was antagonized using neostigmine (0.05 mg/kg) and atropine (0.02 mg/kg).

2.1. Measurements

Demographic data, SAP, DAP, mean arterial pressure (MAP) and HR were recorded before injection of the study drug (baseline), just before initiating laryngoscopy and tracheal intubation (time 0) and at 1 min intervals up to 5 min thereafter.

2.2. For baby assessment

The neonatal outcome was assessed by using Apgar score at 1, 5 and 10 min after delivery and analysis of umbilical artery blood gases. The time to sustained respiration, the need for ventilator assistance and neonatal intensive care unit (NICU) admission were recorded.

2.3. Statistical analysis

Calculation of sample size depended on SAP changes with laryngoscopy and endotracheal intubation. Based on the results of our pilot study on 10 patients allocated into two groups (Dexmedetomidine group and Fentanyl group), SAP changes during laryngoscopy and endotracheal intubation were normally distributed with a pooled standard deviation of 16 mmHg and the clinically significant difference between the groups was a 10 mmHg difference. At least 42 patients were needed to detect the difference with a power of 80% and α error of 0.05. The collected data were analyzed using SPSS software statistical computer package version16

(SPSS Inc, Chicago, IL, USA). Quantitative data are presented as mean ± SD and analyzed using student *t*-test for comparison between the two groups. Categorical data are presented as number (*n*) or percentage (%) and analyzed using Chi-square test (X^2) for comparison between the two groups. $P < 0.05$ was considered statistically significant.

3. Results

44 patients were enrolled (Fig. 1) in each group. In comparison between both groups, there were no statistical significant differences as regard to (Table 1) maternal age, weight, antihypertensive drugs gestational age, newborn weight and parity ($P > 0.05$).

SAP, DAP and MAP (Figs. 2 and 3) showed no statistically significant difference in both groups at baseline values ($P > 0.05$).

In dexmedetomidine group, blood pressure measurements significantly decreased at 10 min after infusion of the dexmedetomidine and they underwent more decrease with induction of general anesthesia as compared to the baseline values. After endotracheal intubation, blood pressure values increased as compared to the pre-induction ones but remained significantly lower than the baseline and returned back to the pre-induction values within 2 min.

As regard to the changes of blood pressure in fentanyl group; blood pressure values insignificantly decreased after administration of fentanyl ($P > 0.05$) and underwent significant decrease with induction of general anesthesia as compared to the baseline value ($P < 0.05$). After endotracheal intubation, blood pressure significantly increased as compared to the baseline and to the pre-induction values ($P < 0.05$). Then blood pressure returned back to the baseline value within 3 min and to the pre-induction value within 4 min.

In comparison between the two groups, blood pressure values were statistically lower in the dexmedetomidine group throughout the study period except baseline ($P < 0.05$).

In dexmedetomidine group, HR measurements (Fig. 4) significantly decreased after drug infusion and remained significantly lower than the baseline value after endotracheal intubation ($P < 0.05$). In patients received fentanyl, HR values decreased after administration of fentanyl then increased after laryngeoscopy and endotreacheal intubation as compared to the baseline value ($P < 0.05$). HR returned back to baseline value within 4 min and

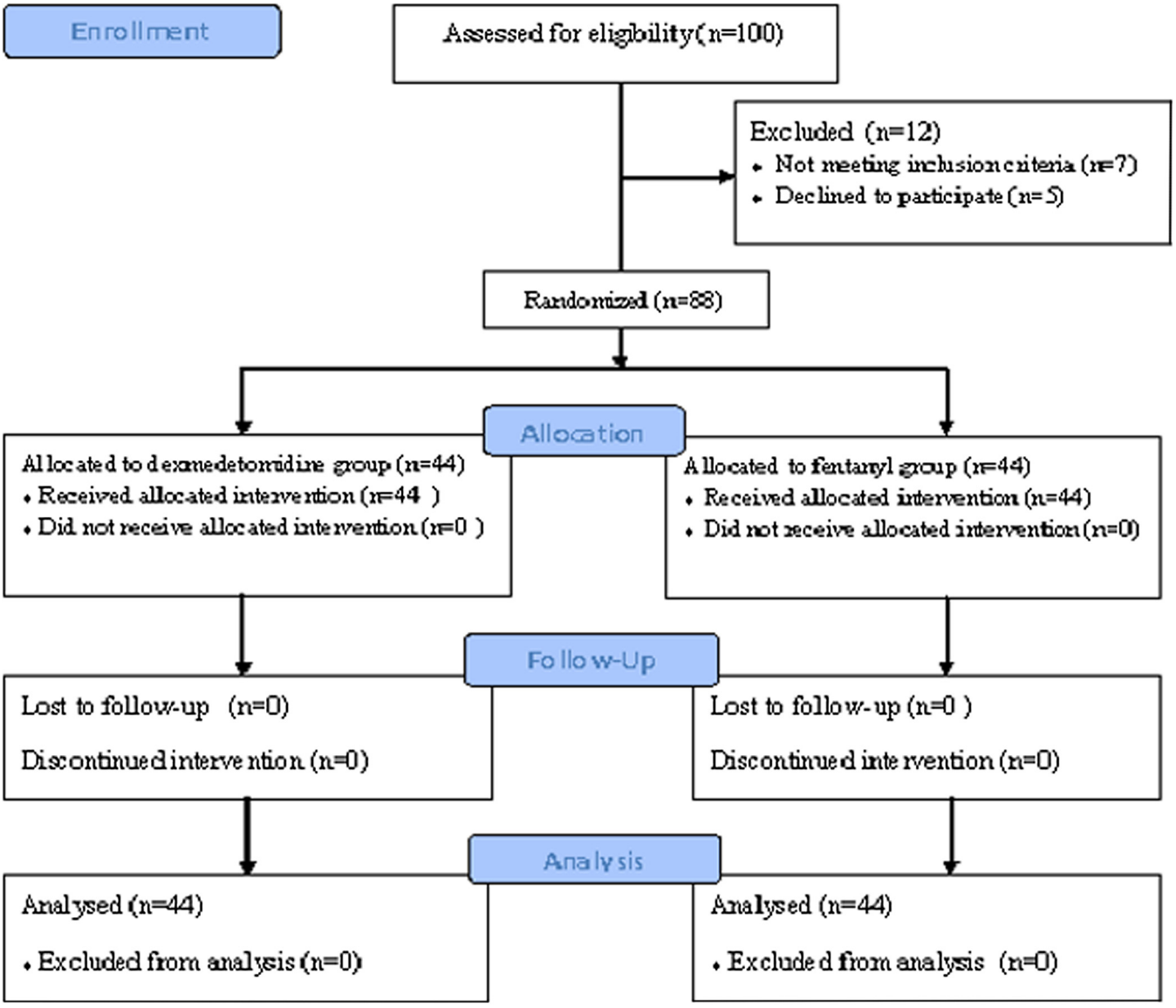

Fig. 1. CONSORT Flow Diagram of participants through each stage of a randomized trial.

Table 1
Patient characteristics and perioperative data presented as mean ± SD or number of patients (%).

		Dexmedetomidine group	Fentanyl group	P value
Maternal age (years)		27.86 ± 5.25	28.3 ± 4.83	0.689
Maternal weight (kg)		84.23 ± 7.91	82.3 ± 8.04	0.259
Parity	Primi	24 (54.5%)	23 (52.3%	0.831
	multi	20 (45.5%)	21 (47.7%)	
Methyldopa		44 (100%)	44 (100%)	1.0
MgSO4 therapy		44 (100%)	44 (100%)	1.0
Hydralazine		19 (43.2%)	17 (38.6%)	0.665
Gestational age (week)		34.95 ± 1.9	34.84 ± 1.9	0.776
Newborn weight(gm)		2203.86 ± 459.44	2149.09 ± 461.82	0.578

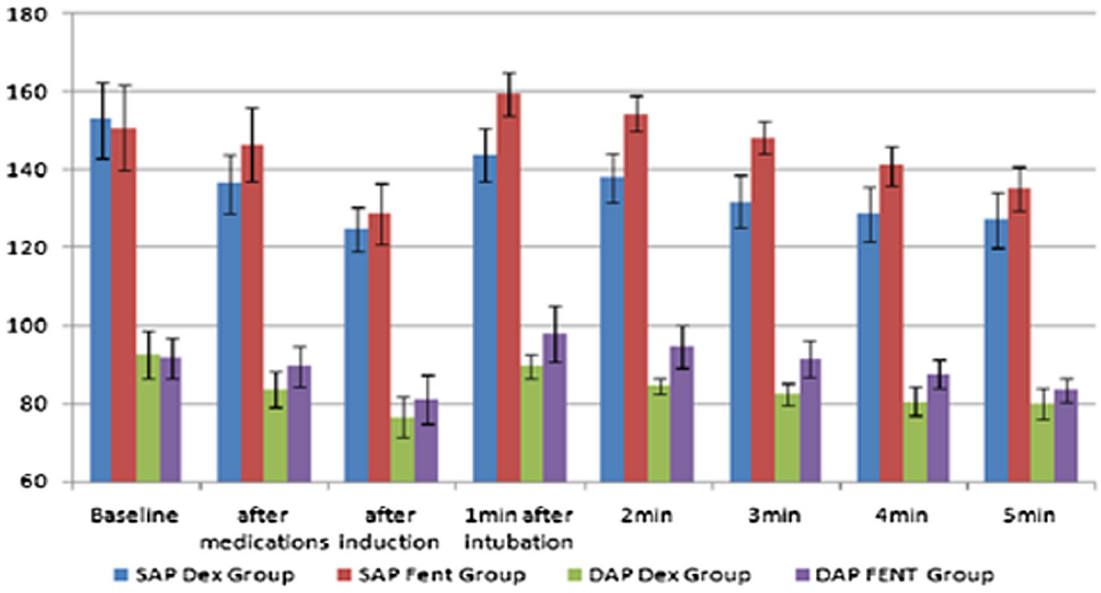

Fig. 2. Systolic and diastolic blood pressure changes in the two studied groups.

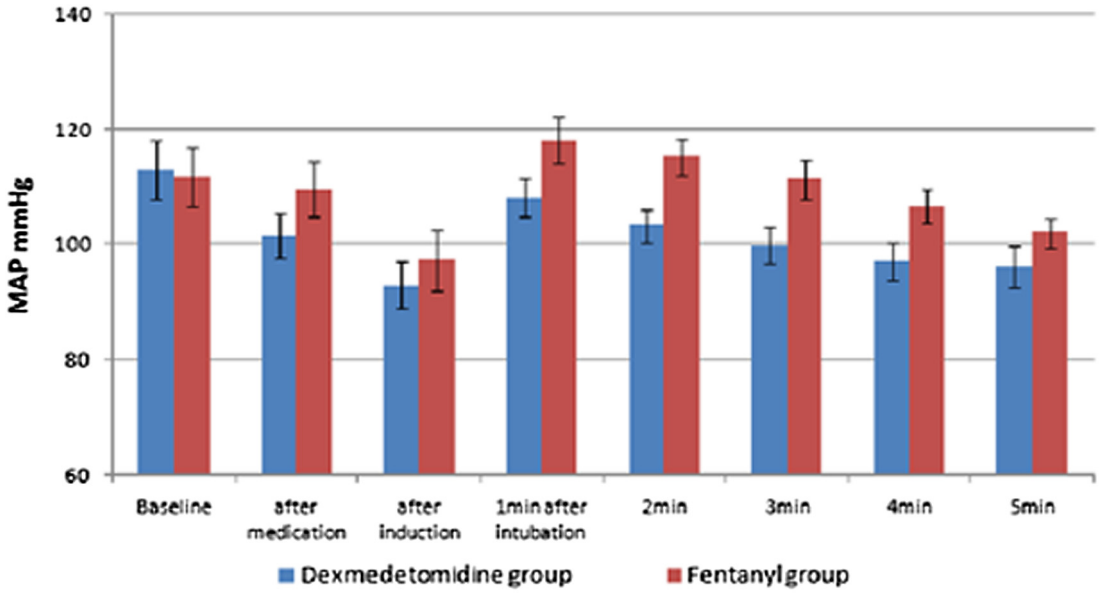

Fig. 3. Mean arterial blood pressure changes in the two studied groups.

to the pre-induction value within 5 min after endotracheal intubation.

Apgar score at 1 min, 5 min and 10 min (Table 2) was comparable between both groups (P > 0.05). Apgar score at 1 min, was <7 in 15 patients (34.1%) in dexmedetomidine group and 18 patients (40.9%) in fentanyl group (P > 0.05). 2 patients (4.5%) in dexmedetomidine group had Apgar score less than 7 at 5 min as compared to 3 patients (6.8%) in Fentanyl group (P > 0.05). 11

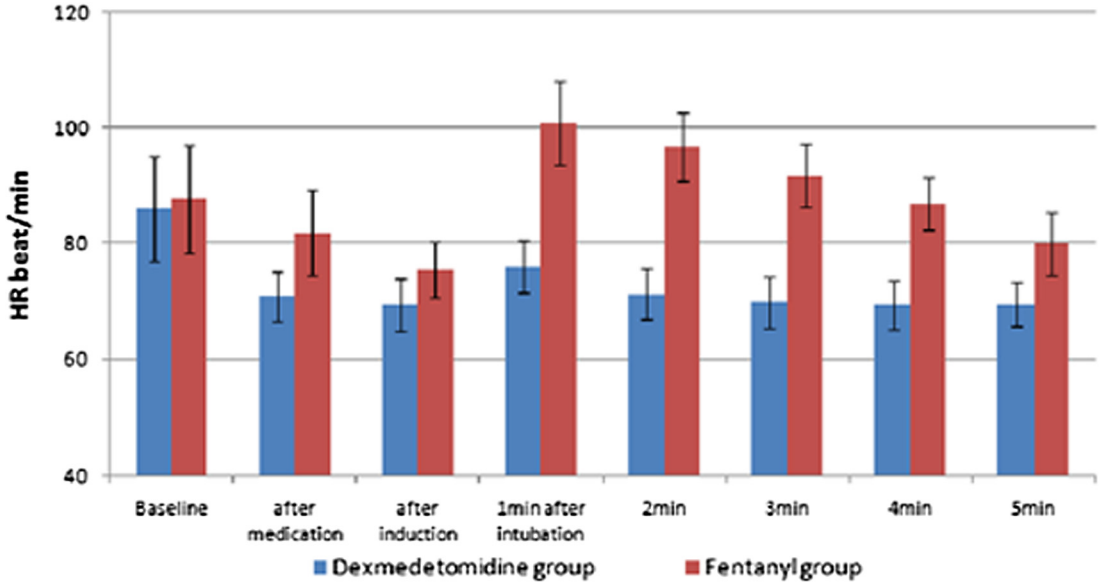

Fig. 4. Heart rate changes in the two studied groups.

Table 2
Apgar score and umbilical artery blood gases; data presented as mean ± SD.

		Dexmedetomidine group	Fentanyl group	P value
Apgar Score	At 1 min	6.93 ± 1.35	6.52 ± 1.15	0.130
	At 5 min	8.66 ± 1.06	8.77 ± 1.14	0.628
	At 10 min	9.70 ± 0.85	9.66 ± 0.89	0.807
Umbilical artery blood gases	PH	7.29 ± 0.02	7.29 ± 0.02	0.780
	PCO2	48.86 ± 1.52	49.48 ± 1.85	0.093
	PO2	22.64 ± 1.14	22.30 ± 1.09	0.156
	HCO3	23.03 ± 0.25	23.31 ± 1.36	0.182
	Base excess	−2.75 ± 0.21	−2.81 ± 0.17	0.195

neonates (25%) in dexmedetomidine group and 13 neonates (29.5%) in fentanyl group were admitted to NICU ($P > 0.05$). One neonate in each group needed endotracheal intubation.

As regard to umbilical arterial blood gases analysis in both groups; pH, PCO_2, PO_2, HCO_3 and base excess were not statistically significant between both groups ($P > 0.05$).

Two parturient had bradycardia in dexmedetomidine group, and treated with i.v. bolus of atropine 0.5 mg. One parturient in each group had hypotension and treated by increasing i.v. crystalloid infusion without the need to ephedrine bolus.

4. Discussion

The results of our research showed that the blood pressure and HR significantly reduced after dexmedetomidine infusion as compared to the baseline values. This significant reduction of the measured hemodynamic variables was maintained after laryngoscopy and endotracheal intubation.

The action of dexmedetomidine mediated through the activation of α2 adrenergic receptors which in turn decrease the sympathetic outflow, [14] dexmedetomidine has also anxiolytic, analgesic and sedative effects [17].

This finding is consistent with the results of EL-Tahan and colleagues [18] who studied the effect of administration of dexmedetomidine in doses of 0.4 and 0.6 μg kg^{-1} h^{-1} during caesarean section and they found that dexmedetomidine is effective in attenuating the hemodynamic and hormonal response without any adverse effect on the neonatal outcome. Li and colleagues [19] compared the effects of remifentanil (a loading dose of 2 μg kg^{-1} over 10 min follow by a constant infusion of 2 μg kg^{-1} h^{-1} till about 6 min before fetal delivery) and dexmedetomidine (a loading dose of 0.4 μg kg^{-1} over 10 min follow by a constant infusion of 0.4 μg kg^{-1} h^{-1} till about 6 min before fetal delivery) when used in general anesthesia for pregnant females underwent caesarean section. They concluded that dexmedetomidine is effective in blunting hemodynamic responses to endotracheal intubation as well as it is safe for the neonates.

Shah and co-workers [20] used dexmedetomidine (a loading dose of 1 μg kg^{-1} over 10 min followed by a maintenance infusion at 0.7 μg kg^{-1} h^{-1}) as sedative during awake fiberoptic intubation in pregnant female with history of Klippel-Feil Syndrome with congenital fusion of their cervical vertebrae posted for caesarean section. Toyama and colleagues [21] used dexmedetomidine for attenuation of hemodynamic response during induction and emergence of general anesthesia in pregnant female 32 weeks' gestation with history of primary pulmonary hypertension during caesarean section.

Dexmedetomidine had reported to attenuate the cardiovascular response during airway management in several studies other than caesarean section. Sezen and co-workers [22] concluded that there was better hemodynamic stability with dexmedetomidine than midazolam in hypertensive patients. Basar and co-workers [14] concluded that dexmedetomidine at doses of 0.5 μg kg^{-1} when given 10 min before induction of anesthesia can blunt the cardiovascular response to intubation with no changes in recovery score. The attenuation of hemodynamic response to air way management by dexmedetomidine is reported in other studies [23–25].

Administration of fentanyl (1 μg kg^{-1}) 3 min before induction of general anesthesia resulted in insignificant decrease in the blood pressure and significant decrease in the HR as compared to the baseline values. Laryngoscope and endotracheal intubation was associated with significant alteration of the hemodynamic variables.

In agreement with our finding Pournajafian and co-workers [26] compared the effectiveness of remifentanil and fentanyl in the attenuation of hemodynamic response to endotarcheal intubation during induction of general anesthesia for pre-eclamptic patients during caesarean section, they found that blood pressure and heart rate increased after intubation in fentanyl group. Hussain and sultan [27] found that fentanyl (2 μg kg^{-1}) given 2 min before laryngoscopy and endotracheal intubation was inadequate to prevent the increase in blood pressure and heart rate. On the other hand, fentanyl attenuated the hemodynamic response to endotracheal intubation in other studies; either caesarean section [28] or other operations [29,30].

There was no significant difference between both groups as regards the neonatal outcome.

Apgar score at 1, 5 and 10 min and umbilical artery blood gases were used to assess the neonatal outcome. Apgar score was insignificantly different between both groups at all times of assessment. Apgar score at 5 min was less than 7 in 2 neonates in dexmedetomidine group and 3 neonates in fentanyl group. All the five neonates were premature with gestational age 32 weeks or less. Dexmedetomidine characterized by its higher lipophilicity which leads to greater placental retention and less dexmedetomidine transport to the fetus [31]. Dexmedetomidine was used in some animal studies during labour and surgical delivery [32,33]. Tariq and colleagues [32] studied the effects of subchronic versus acute exposure to dexmedetomidine on fetal development in rats. They reported that exposure of the pregnant rat to single acute dose of dexmedetomidine (20 μg kg^{-1}) at anticipated labour time is completely safe for mother and neonate. While, chronic use of dexmedetomidine for pregnant rat resulted in significant reduction of the birth weight and crown-rump length without any effect on the postnatal development, including neurological status and body weight gain. Uemura and colleagues [33] studied the effect of intravenous infusion of clinical relevant dose of dexmedetomidine on pregnant sheep underwent preterm surgical deliveries. They concluded that dexmedetomidine causes maternal sedation with no effect on the fetal physiological status.

Dexmedetomidine was used in previous studies in human during caesarean section and for labour analgesia without any harmful effect on the neonatal outcome [18–21,34,35].

Use of opioids during induction of anesthesia in caesarean section is matter of challenge. Because of lipid solubility of Opioids, they can be transported easily to the fetus and cause adverse effects like neonatal respiratory depression [28].

Maghsoudloo and co-workers [28] reported the use of I.V. fentanyl at doses of (1 μg kg^{-1}) 3 min before induction of general anesthesia without adverse effects on the neonatal outcome. Pournajafian and co-workers [26] concluded the safe use of fentanyl (50 μg) before induction of general anesthesia for pre-eclamptic patients during caesarean section on the neonatal outcome.

There are some limitations of our study, first, the present study depends on the hemodynamic parameters for assessment of the attenuation of cardiovascular response to airway management without measuring the blood level of catecholamine and cortisone. Second, the documentation of hemodynamic parameters was limited to 5 min after intubation and the extubation response did not documented. Third, we did not assess the quality of postoperative analgesia.

5. Conclusions

Dexmedetomidine (0.5 μg kg^{-1}) given over 10 min before induction of general anesthesia significantly reduced the measured hemodynamic variables compared to baseline values. Dexmedetomidine successfully attenuated the intubation stress response and provided a significant hemodynamic stability more than fentanyl (1 μg kg^{-1}) which given 3 min before the induction of general anesthesia in sever pre-eclamptic patients. Neither drug was associated with any harmful neonatal outcome.

Assistance with the article

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Conflicts of interest

None.

Presentation

None.

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