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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