EXPERIMENTAL STUDY

The effects of dexmedetomidine on pulmonary artery pressure in experiment

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Abstract: *Aim:* The primary purpose of this study is to assess the effects of dexmedetomidine (DEX) infusion on pulmonary artery pressures (PAP), heart rate (HR), and mean arterial pressure (MAP) in pigs. The secondary purpose is to evaluate whether DEX infusion via the pulmonary artery has any beneficial effect over the peripheral IV route.
Materials and methods: Sixteen healthy male pigs (25–35 kg) scheduled for laparoscopy training were used in this study. The animals were randomly allocated into two groups: Group I (n = 9): A loading dose of 1μg/kg DEX was administered over 10 minutes followed by an infusion of 0.5 μg/kg/hr for one hour via the pulmonary artery catheter. Group II (n = 7): A loading dose of 1 μg/kg DEX was administered over 10 minutes followed by an infusion of 0.5 μg/kg/hr for one hour via the peripheral venous catheter. Mean PAP, HR, MAP, SpO_2, and $ETCO_2$ were recorded at 5, 10, 15, 30, 45, and 60 minutes after the initiation of the DEX infusion.
Results: Heart rate and MAP were similar in both groups at all time points. Also, neither the HR nor the MAP deviated from the basal values in Groups I and II at any time point. The mean PAP values were similar in Groups I and II, and in Group I, the mean PAP values were similar to Group I's basal value at all time points. However, in Group II, the mean PAP values at 5, 45, and 60 minutes were significantly lower than Group II's basal value (p = 0.023, p = 0.041, p = 0.015, respectively).
Conclusion: DEX infusion did not elevate the mean PAP and the results from the administration of DEX through the peripheral vein and pulmonary artery were similar *(Tab. 3, Ref. 13)*. Text in PDF *www.elis.sk.*
Key words: pulmonary artery pressure, dexmedetomidine, pig.

A specific α-2 adrenergic receptor agonist dexmedetomidine (DEX) is used for sedation and as an analgesic during the anesthesia process. It produces sympatholysis through the activation of the α-2 postsynaptic adrenergic receptors of the central nervous system and sympathetic nerves, which leads to decreased norepinephrine turnover, central sympathetic outflow, heart rate, and blood pressure. However, it produces both vasoconstriction of the α-2 receptors on vascular smooth muscle cells and vasodilatation through the stimulation of the α-2 receptors on vascular endothelial cells (1, 2). It also shows analgesic properties through the activation of α-2-adrenergic receptors of the spinal cord's dorsal horn, inhibiting the release of substance P (3).

Although it has been used in several clinical procedures, such as procedural sedation, an addition to general anesthesia, treatment of arrhythmias, and withdrawal symptoms from opioids and benzodiazepines (2), there is limited data about how DEX affects pulmonary artery pressures (PAP).

In a study performed by Chrysostomou et al (4), the use of DEX alone or in combination with a low dosage of conventional sedatives and analgesics was well tolerated and provided an adequate level of sedoanalgesia in both intubated and non-intubated infants

and neonates after cardiac surgery (4). The results of the study by Lazol et al (2) conducted in 22 children undergoing surgery for congenital heart disease suggest that postoperative DEX infusion for sedoanalgesia was not associated with any increase in PAP.

The primary purpose of this study is to assess the effects of DEX infusion on PAP, HR, and MAP in pigs. The secondary purpose is to evaluate whether DEX infusion via the pulmonary artery has beneficial effects over peripheral infusion.

Materials and methods

Following the approval of the Ethics Committee for Animal Research at Gazi University, 16 healthy 4–5 month old, 25–35 kg male pigs that were scheduled for laparoscopy training course were used in this study. After intramuscular sedation with ketamine (15mg/kg) and xylazine (2 mg/kg), the pigs' ear veins were cannulated, and 5mL/kg of normal saline infusion was started for all the animals. Peripheral oxygen saturation (SpO_2), HR, MAP, and end-tidal carbon dioxide ($ETCO_2$) (following endotracheal intubation) were measured. Following the administration of thiopental sodium (7 mg/kg), all the pigs were intubated without a neuromuscular blocker, and mechanical ventilation was initiated to maintain $ETCO_2$ at 30–35 mmHg. Anesthesia was managed using 1 % isoflurane in oxygen/air (50 %/50 %). The right internal jugular vein was surgically explored after upright positioning, and a pulmonary artery catheter (four-lumen thermodilution catheter, 8F, 110 cm; Abbott Laboratories, Zwolle, the Netherlands) was placed using the waveform monitoring technique.

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After the mean PAR, HR, MAP, $ETCO_2$, and SpO_2 basal values were recorded, the animals were randomly allocated into two groups:

- Group I (n = 9): A loading dose of 1μg/kg of DEX was administered for 10 minutes. This dose was followed by an infusion of 0.5μg/kg/hr for one hour via a pulmonary artery catheter.
- Group II (n = 7): A loading dose of 1μg/kg of DEX was administered for 10 minutes. This infusion was followed by an infusion of 0.5μg/kg/hr for one hour via a peripheral venous catheter.

The mean PAP, HR, MAP, $ETCO_2$, and SpO_2 were identified and recorded at 5, 10, 15, 30, 45, and 60 minutes after the initiation of the DEX infusion.

The animals were left for the laparoscopy training course after all the study protocols were recorded. At the end of the course, all the animals were euthanatized using a high dose of thiopental sodium.

Statistical analysis

The statistical analyses were performed using SPSS 17.0 software and $p < 0.05$ was considered statistically significant. Variations in PAP, MAP, and HR parameters between study groups were assessed using the Kruskal-Wallis test. The Bonferroni-adjusted Mann-Whitney U-test was conducted after a significant Kruskal-Wallis to determine which group differed from the other. PAP, MAP, and HR parameters were analyzed using repeated-measures analysis of variance (ANOVA) with Bonferroni's adjustment. The results were expressed as mean±standard deviation (mean±SD) and minimum–maximum (min–max).

Results

All the pigs had comparable ages and body weights. The heart rate and MAP were similar in both groups at all time points. Also, HR and MAP of Groups I and II did not deviate from the basal values at any time point (Table I). The mean PAP values were similar in Groups I and II at all time points. The mean PAP values at all time points were similar to the basal value in Group I. However, in Group II, the mean PAP values at 5, 45, and 60 minutes were significantly lower than the basal values ($p = 0.023$, $p = 0.041$, $p = 0.015$, respectively).

Discussion

In the current study, the effects of DEX administered through either a peripheral vein or pulmonary artery on HR, MAP, and MPAP were comparable. A biphasic cardiovascular response is a well-known haemodynamic effect of DEX. After a 1μg/kg bolus dose of DEX, the initial response in healthy adults is a transient increase in BP, due to the stimulation of vascular smooth muscle α-2 receptors, followed by a reflex decrease in HR (5). Hammer et al (6) reported a similar biphasic response in children after a bolus dose of DEX. Potts et al (7) recommended a small bolus dose of 0.5 μg/kg DEX over 10 minutes to avoid these haemodynamic changes. Although the bolus dose of DEX used in our study was two times the dose used in the Potts et al. study, the infusion time was 10 minutes. The slow bolus dose infusion rate prevented the biphasic response to DEX in our study, which is similar to Potts et al.

Tab. 1. Time-dependent changes in the HR of the animals.

Heart Rate (beat/min)	Group I (n=9)	Group II (n=7)	p
HR_c	88.67±27.94 (68–152)	106.67±28.67 (72–135)	0.151
HR_5	76.17±22.25 (52–130)	85.00±24.12 (54–106)	0.646
HR_{10}	70.91±21.09 (46–123)	81.83±22.31 (54–113)	0.350
HR_{15}	70.89±16.79 (49–95)	82.00±21.95 (53–114)	0.328
HR_{30}	74.00±19.34 (49–114)	89.25±27.11 (52–117)	0.199
HR_{45}	70.14±13.86 (52–91)	90.50±28.03 (52–119)	0.164
HR_{60}	75.25±13.22 (53–90)	84.83±25.92 (51–122)	0.414

HR_c – heart rate control value, mean±SD, (min–max)

Tab. 2. Time-dependent changes in the MAP of the animals.

MAP (mmHg)	Group I (n=9)	Group II (n=7)	p
MAP_c	69.00±17.06 (40–94)	68.29±12.50 (53–89)	0.837
MAP_5	56.36±17.77 (30–84)	59.71±15.34 (45–87)	0.791
MAP_{10}	59.36±14.85 (38–78)	55.14±15.02 (32–78)	0.724
MAP_{15}	58.25±13.89 (31–72)	53.43±12.56 (30–69)	0.336
MAP_{30}	57.0±14.02 (34–82)	57.20±8.76 (47–78)	1.000
MAP_{45}	53.00±16.16 (34–81)	56.60±12.58 (45–75)	0.524
MAP_{60}	52.14±17.48 (31–78)	56.00±13.53 (30–69)	0.710

MAP_c – Mean arterial pressure control value, mean±SD, (min–max)

Tab. 3. Time-dependent changes in the mean PAP (MPAP) values.

MPAP (mmHg)	Group I (n=9)	Group II (n=7)	p
$MPAP_C$	22.33±8.11 (10–38)	18.60±2.70 (16–23)	0.298
$MPAP_5$	18.50±5.21 (8–26)	15.60±2.07& (13–18)	0.092
$MPAP_{10}$	19.56±6.27 (9–28)	16.40±2.88 (13–20)	0.298
$MPAP_{15}$	16.75±5.26 (9–24)	15.60±3.36 (11–18)	0.833
$MPAP_{30}$	18.25±4.09 (13–24)	15.20±2.59 (12–18)	0.284
$MPAP_{45}$	17.00±6.59 (11–30)	14.60±3.58* (12–19)	0.622
$MPAP_{60}$	18.00±5.24 (12–24)	14.40±3.91* (12–21)	0.122

$MPAP_c$ – Mean pulmonary artery pressure control value, * $p < 0.05$ (compared $MPAPc$), mean±SD, (min–max)

In Deutsch and Tobias's (8) study of 80 pediatric patients receiving maintenance anesthesia with either 1 MAC of sevoflurane or desflurane, the addition of intravenous (IV) DEX (0.5 μg/kg) administered over 5 min resulted in a lower HR, which was greater in patients anesthetized with sevoflurane than those receiving desflurane. Although both sBP and dBP decreased following DEX, they found no

evidence of differences in sBP and dPB between the two groups. Likewise, because there was no change in the PECO$_2$ values, there is no evidence that DEX had any effect on respiratory function. These data provided additional information about the hemodynamic and ventilatory changes following the intraoperative use of DEX in children.

DEX has been increasingly used in the operating room as an addition to general anesthesia and in the ICU for sedoanalgesia. Off-label use of DEX for sedation and analgesia, especially after complex pediatric cardiac surgical procedures has gained attention. In a pioneer study by Lazol et al (2), DEX infusion elevated PAP in 22 pediatric patients after cardiothoracic surgery via echocardiography. A significant decrease from the basal value in PAP was found at 6 minutes and 1 hour after infusion. In the study, sedation using DEX infusion after cardiac surgery is a successful treatment for high risk patients with pulmonary hypertension (2).

One of the sedation modalities for pediatric patients after cardiac surgery in our institute is DEX infusion. The results of the studies evaluating the effects of DEX infusion for the treatment of pulmonary hypertension are controversial, and the exact mechanism of the effect is unclear. Therefore, we sought to evaluate DEX infusion's effects on PAP. We also evaluated whether DEX infusion via the pulmonary artery has any beneficial effects over the peripheral IV route.

Our results suggest that the administration of DEX through the pulmonary artery or peripheral vein is not associated with an increase in pulmonary artery pressure. In fact, after its administration, DEX decreased MPAP at all time points. However, DEX administered via the peripheral vein caused statistically significant decreases at the 5th, 45th, and 60th minutes compared to basal value.

There are several reports on the successful use of DEX for the sedation of patients with pulmonary hypertension (9–11). Nathan et al (9) used DEX in a 16-year-old patient with pulmonary hypertension, pneumonia, and respiratory failure. Sedation with DEX relieved the pleuritic pain and relieved anxiety. The authors concluded that sedation with DEX improved respiratory status and prevented endotracheal intubation without any additional adverse effects. Shinohara et al (10) reported a successful management of a sedation procedure in a 21-year-old patient with pulmonary hypertension during an ilioinguinal/iliohypogastric block herniorrhaphy. But et al (11) showed that compared to a placebo group, the group of patients with pulmonary hypertension undergoing mitral valve replacement surgery that received the pre-operative administration of DEX decreases the fentanyl requirement and effectively decreases MAP, MPAP, and pulmonary capillary wedge pressure (PCWP).

The direct pulmonary artery vasodilating properties of DEX have not been identified. The decrease in PAP during DEX infusion is the result of sympatholysis via the activation of α-2 adrenergic receptors. Snapir et al (12) also showed that the decrease in PAP and blood pressure following DEX infusion in healthy volunteers is related to the decline in the circulating cathecholamines due to central sympatholysis (12). Ebert et al (13) performed a study in volunteers, and 0.7 and 1.2 ng/ml plasma concentrations of DEX decreased the plasma norepinephrine concentration by more than 50 %. The effects of DEX on PAP may be beneficial to patients with elevated circulating catecholamine levels who had undergone cardiothoracic surgery or an exposed cardiopulmonary bypass.

There are several limitations in the study. The subjects in the study did not have pulmonary hypertension, and DEX infusion was started under general anesthesia. Therefore, it is difficult to generalize the results of the study for patients with pulmonary hypertension and for postoperative patient who received DEX infusion for sedation and analgesia. Another limitation of the current study is the lack of data on catecholamine levels, which prevents us from commenting on the most possible mechanism of action of DEX. Also, the study does not have any data about the postoperative course of the surgical procedures.

Conclusion

In this pilot study, DEX infusion did not elevate MPAP, and the effects of DEX administration through the peripheral vein and pulmonary artery were similar. Therefore, DEX infusion may have potential benefits in patients with pulmonary hypertension. However, further studies in subjects with the pulmonary hypertension are needed to support our findings.

References

1. Tobias JD, Gupta P, Naguib A, et al. Dexmedetomidine: Applications for the pediatric patient with congenital heart disease. Pediatr Cardiol 2011; 32: 1075–1087.

2. Lazol JP, Lichtenstein SL, Jooste EH, et al Effect of dexmedetomidine on pulmonary artery pressure after congenital cardiac surgery: A pilot study. Pediatr Crit Care Med 2010; 11 (5): 589–592.

3. Gazit AZ. Dexmedetomidine and pulmonary artery pressure in the pediatric cardiac surgery patient – A new insight. Pediatr Crit Care Med 2010; 11 (5): 634–635.

4. Chrysostomou C, Sanchez De Toledo J, Avolio T et al. Dexmedetomidine use in a pediatric cardiac intensive care unit: Can we use it in infants after cardiac surgery? Pediatr Crit Care Med 2009; 10 (6): 654–660.

5. Sulaiman S, Karthekeyan RB, Vakamudi M et al. The effects of dexmedetomidine on attenuation of stress response to endotracheal intubation in patients undergoing elective off-pump coronary artery bypass grafting. Ann Card Anaesth 2012; 15 (1): 39–43.

6. Hammer GB, Drover DR, Jackson E. The effects of dexmedetomidine on cardiac electrophysiology in children. Anesth Analg 2008; 106: 79–83.

7. Potts AL, Anderson BJ, Holford NH et al. Dexmedetomidine hemodynamics in children after cardiac surgery. Pediatr Anesth. 2010; 20: 425–433.

8. Deutsch E, Tobias JD. Hemodynamic and respiratory changes following dexmedetomidine administration during general anesthesia: Sevoflurane vs desflurane. Pediatr Anesth 2007; 17: 438–444.

9. Nathan AT, Marino BS, Hanna B et al. Novel use of dexmedetomidine in a patient with pulmonary hypertension. Pediatr Anaesth 2008; 18: 782–784.

10. Shinohara H, Hirota K, Sato M et al. Monitored anesthesia care with dexmedetomidine of a patient with severe pulmonary arterial hypertension for inguinal hernioplasty. J Anesth. 2010; 24: 611–613.

11. But AK, Ozgul U, Erdil F et al. The effects of preoperative dexmedetomidine infusion on hemodynamics in patients with pulmonary hypertension undergoing mitral valve replacement surgery. Acta Anaesthesiol Scand 2006; 50: 1207–1212.

12. Snapir A, Posti J, Kentala E et al. Effects of low and high plasma concentrations of dexmedetomidine on myocardial perfusion and cardiac function in healthy male subjects. Anesthesiology 2006; 105: 902–910.

13. Ebert TJ, Hall JE, Barney JA et al. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000; 93: 382–394.