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Dexmedetomidine versus Fentanyl in Children Undergoing Central Venous Catheter Placement at the Pediatric Intensive Care Unit: A Randomized Double-Blind Clinical Trial

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Abstract

Background: The amount of sedation required for children in the pediatric intensive care unit (PICU) is a usually challenging issue. Fentanyl is a commonly used sedative in PICU, but respiratory depression limits its use. Dexmedetomidine (DEX) is an effective sedative and anesthetic agent with negligible respiratory depression and hemodynamic stability.This study was aimed to assess the effects of using DEX as a sedative in comparison to fentanyl.

Methods: We conducted a randomized double-blind clinical trial on children aging 1 month to 18 years who were required central venous catheter at PICU. The patients were randomized into the DEX and fentanyl (loading dose 1 mcg/kg and 1 mcg/kg/h for continuous infusion) groups. The primary outcome was defined as the time to achieve Ramsay Sedation Scale (RSS) ≥3, along with the safety outcome.

Results: A total of 55 patients were recruited for the analysis between July 7 and December 30, 2020. The two groups were comparable at baseline. There was no statistical difference in the number of patients (63% in DEX and 50% in fentanyl group p=0.39) and the time of reaching RSS≥3 (10 min for DEX and 15 min for fentanyl group p=0.098). Furthermore, the catheterization time between the two groups was not different when the agents were administered individually or with propofol (15 min for DEX and 17.5 min for fentanyl, p=0.225, and 22.5 for DEX and 30 min for fentanyl group, p=0.075 respectively); neither was the safety profile significantly different in the two groups.

Conclusions: This study found that DEX as a primary sedative is non-inferior to fentanyl, and it could facilitate sedation alone or in combination with propofol.

Key Words: Dexmedetomidine, Fentanyl, Pediatrics, Sedation.

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1- INTRODUCTION

Central venous catheter (CVC) placement is an invasive procedure which is often used in intensive care units for long-term intravenous care, multiple sampling, central venous pressure measurement, convenient administration of fluids, blood products, as well as bulky or high-density solutions, and when other techniques fail in obtaining intravenous access. Various sedatives, including fentanyl, midazolam, and propofol, are commonly used for sedation and reduction of pain caused by CVC placement (1, 2).

Dexmedetomidine (DEX) is an alpha-adrenergic receptor agonist with a structure similar to clonidine, yet it has a greater affinity and sensitivity to α2 than to α1 receptor subtypes. In addition, it binds to both peripheral and central α2 receptors. DEX also has sedative, analgesic, anesthetic, and anxiolytic effects with favorable safety (3, 4). Since clonidine is only available as an oral tablet in our setting, its use in the PICU is limited. The tendency to use DEX as a sedative and neuro-protective drug has, recently, increased, as animal studies have shown its neuroprotective effects against ischemia, hypoxemia, and cell death (5). DEX has been widely used for anesthesia and analgesic purposes (6), and has comparable effects to benzodiazepines; it is associated with a faster onset of action and fewer side effects on the respiratory system as well as hemodynamic parameters. There is some evidence for its efficacy as a single agent or in combination with other drugs in non-invasive procedures such as computed tomography scan (CT), magnetic resonance imaging (MRI), and electroencephalogram (EEG) in children (7-12).

Fentanyl is a synthetic opioid, which is commonly used in children for sedation and analgesia due to its known pharmacologic properties and less adverse effects on the cardiovascular system. Although fentanyl has favorable effects on hemodynamic status, its effects on respiratory depression can be serious (13-15).

Given the beneficial effects and tolerable safety profile of DEX in adults as well as the insufficient relevant data on children undergoing invasive procedures, the aim of this study was to evaluate the efficacy and safety of this agent in comparison to fentanyl for CVC insertion in a pediatric setting.

2- METHODS

This randomized double-blinded clinical trial was conducted in a tertiary 12-bed pediatric intensive care unit (PICU) in Ibn Sina Hospital, Sari, and northern Iran.

All children aged one month to 18 years who were admitted to the PICU and needed CVC insertion were evaluated for recruitment. Since the experience of DEX in children is limited and the safety concerns for this indication are not completely clear, the patients with hypotension, hypertension, apnea and arrhythmia were excluded. Other exclusion criteria were scoring 4 based on the ASA (American Society of Anesthesiologists) physical status classification, renal failure, history of cardiac surgery, shock state, or concomitant use of muscle relaxants. If the participants had been taking other sedatives, their administration was terminated; we also considered the right washing period for the participants based on the medicine's half-life (after 4-5 half-life), and only then started the intervention.

A randomization table was used to put the participants of both DEX and fentanyl groups in a 1: 1 ratio. When the physician determined the need for CVC replacement, a pharmacist researcher removed the medicine syringes out of the sealed and numbered envelopes. The medicine was prepared in the same size, color, and shape

of syringes. In order to blind the study, the medicine was prepared in a similar syringe. The physician, pharmacist, nurses, patients or their parents, and statistician were not informed of the group assignment.

The physician performed the catheterization without knowing the type of drug, and the outcome assessor evaluated and recorded the sedation-related indicators under the physician's supervision. After the procedure was completed and the outcomes (maximum 1 hour) were recorded, the type of drug used was determined and recorded in the patient's file. During the procedure, if a severe drug-related complication or a life-threatening condition occurred (such as hypoxemia, apnea and bradycardia), the main researcher was in charge of making the appropriate decision, if necessary.

Before the implantation of CVC, a 12-lead ECG and renal function tests were performed for the patients. Also, the level of Glasgow Coma Scale (GCS), Mean Arterial blood Pressure (MAP), Heart Rate (HR), Respiration Rate (RR), and capillary blood oxygen saturation (O_2-sat) were recorded immediately before starting the interventions. (It should be added that MAP and O_2-sat were measured using the non-invasive oscillometric method and pulse oximetry, respectively).

The control group received fentanyl (Darou Pakhsh pharmaceutical company) at a dose of 1 microgram per kilogram body weight (mic/kg) for 10 minutes as a loading dose. Then, the infusion continued at a rate of 1 mic/kg per hour during catheter insertion. In the intervention group, DEX (EXIR pharmaceutical company) was administered intravenously at a dose of 1 mic/kg for 10 minutes as a loading dose; during catheter insertion, infusion continued at a rate of 1 mcg/kg per hour (16, 17). In both groups, if more sedation was needed (Ramsay Sedation Scale (RSS) ≥3), the loading dose of the group's medication was repeated and drug infusion continued at the same rate and for the same duration. In case of insufficient sedation after two loading doses, intravenous propofol was administered at a dose of 1 milligram per kilogram body weight.

All CVCs were inserted by an expert pediatrician using Seldinger technique and sonographic guidance. Before the procedure, appropriate local anesthesia was made using up to 4 milligrams per kilogram body weight of lidocaine for all cases.

Once the loading dose started, the RSS, MAP, O2-sat, HR, and RR were recorded every 5 minutes until the end of the procedure. Moreover, all participants were followed up 24 hours after catheterization to evaluate any possible adverse effects.

All patients received supplemental oxygen through the nasal cannula, which delivered oxygen at 0.5 liter per minute, during catheter placement. When the O2-sat was between 94-90%, the condition was called transient hypoxia. If the patients' oxygen saturation decreased below 90%, a reservoir bag mask was inserted. The resuscitation facilities were available at the patient's bedside throughout the study.

2-1. Outcome assessment

The primary outcome was the effectiveness of the DEX infusion, defined as the time to RSS≥3 without the need for extra sedation. The safety concerns of therapeutic regimens regarding changes in vital signs including MAP, HR, O_2-sat, and RR were considered the secondary outcomes. Changes more than 20% in MAP, HR, and RR were assumed as adverse events (AEs). In addition, the O2-sat level of 94-90% was defined as transient hypoxemia, and the saturation level lower than 90% was determined as hypoxemia with the need to wear the reservoir bag mask. Moreover, apnea was

reported if the airflow stopped for at least 10 seconds.

2-2. Statistical analysis

To assess effectiveness, we used intention-to-treat analysis for all patients who were given the study drug. Continuous variables were summarized as median (interquartile range) according to the study groups (DEX vs. fentanyl), and the results were compared using a two-sample independent t-test for normally distributed variables or non-parametric alternative, and Mann-Whitney U-test if the values were not normally distributed. Categorical variables were summarized as frequencies and percentages and analyzed using Fisher's exact test and Chi-square test. The effect sizes of the interventions on MAP, was estimated using the generalized estimating equations (GEE) linear model; and the GEE poisson model was applied for analyzing the effect sizes on RR and HR. Additionally, P <0.05 was considered statistically significant, and all analyses were performed using SPSS version 22.

2-3. Sample size

A sample size of at least 26 patients for each group was considered according to the standard deviation (SD) of 1.8 to make a difference of 4 minutes during sedation induction (18) with a power of 80% and the Type I error of 0.05. The sample size was calculated, using the following formula:

$$n_1 = \left(\frac{1+\varphi}{\varphi}\right)\frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\alpha}\right)^2}{\Delta^2} + \frac{z^2{}_{1-\frac{\alpha}{2}}}{2(1+\varphi)}$$

$$\Delta = \frac{\mu_2 - \mu_1}{\sigma}\ ; \varphi = \frac{n_2}{n_1}$$

3- RESULTS

This study was performed between July 7 and December 30, 2020. Totally, 430 patients were admitted to the PICU, among which 95 individuals needed CVC replacement during PICU stay. An overview of this study is shown in **Fig. 1**. The participants were randomly divided into the DEX or fentanyl groups. After randomization, 2 patients in the fentanyl group and 3 patients in the DEX group mistakenly received propofol earlier than determined time of the study protocol, so they were excluded from the study.

Demographic and clinical characteristics were recorded and analyzed. Approximately 53% of children were younger than 5 years, 25% were between 5 and 8 years of age and the rest were older than 8 years old with no significant difference between two groups (p= 0.60). In this study, 60.0% and 71.4% of the children were boys in Dex and fentanyl groups, respectively; and there was no significant difference between the two groups in terms of gender (p=0.51) (**Table 1**).

There was no statistical difference in the number of patients who achieved RSS≥3 in the two groups at different intervals (p=0.387, **Table 2**), yet the patients in the DEX group reached RSS≥3 faster. Thus, the median time for reaching RSS≥3 was 10.00 minutes (IQR, 10.00-15.00) in the DEX group and 15.00 minutes (IQR, 10.00-15.00) in the fentanyl group (p= 0.10).

According to the results of intention-to-treat analysis, the time to reach proper sedation and start the procedure was faster in the DEX group compared to the fentanyl group, but this variation was not statistically significant in the two groups. The median completion time of catheterization was 15.00 minutes (IQR 15.00-17.50) in the DEX group and 17.50 minutes (IQR 15.00-20.00) in the fentanyl group (p=0.22); therefore, the procedure ended earlier in the DEX group than the other group, although it was not statistically significant (**Table 3**).

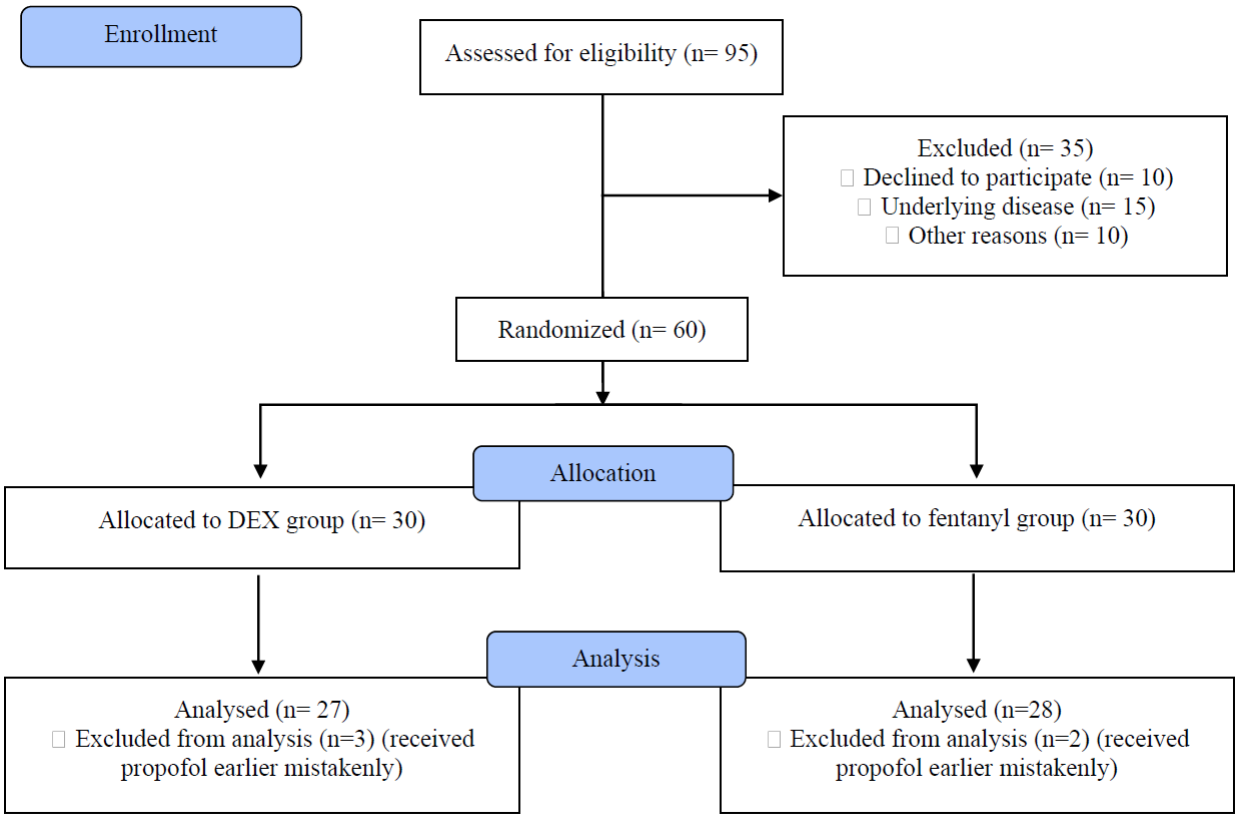

Fig. 1: Consort flow chart

No significant difference occurred between the two groups in terms of needing extra sedation (p=0.337, Table 2). Also, there was no significant difference between the two groups in terms of the median time of reaching the proper sedation and completion time of catheterization after using propofol (p=0.138 and 0.075, respectively).

Vital signs including HR, RR, and MAP were assessed at regular intervals during the study procedure. During the study time in both groups, the HR was significantly different as compared to the baseline (p<0.05, **Fig 2**). The HR average in the DEX group was 0.06 more than that in the fentanyl group, although this difference was not statistically significant (p= 0.26, 95% confidence interval (CI) = -0.04 - 0.165). Compared to the baseline, the RR was also significantly different during the study time in both groups of the study (p<0.05, **Fig 2**). The mean RR in the DEX group was 0.20 more than that in the fentanyl group, and this difference was significant between the groups (p= 0.03, 95% CI= -0.01 - -0.38). Additionally, Compared to the baseline, the HR was significantly different within the groups during the study period (p<0.05). The average of HR in the DEX group was 1.47 higher than that in the fentanyl group, although this difference was not significant (p= 0.67, 95% CI= -5.27 - 8.20).

The observed adverse effects were analyzed in both study groups (**Table 5**), yet no significant differences were seen in this regard. Most of these complications were mild to moderate and did not require any intervention. In addition, all patients were followed up for 24 hours after CVC replacement, and no abnormal condition was associated with the procedure; besides, the RSS and GCS returned to baseline and were fixed there.

Table-1: Baseline demographic and clinical characteristics of the patients

Variables		DEX	Fentanyl	Total	P
Age, month median (IQR)		42 (18-96)	39 (22-95)	42 (21-96)	0. 97
Age, n (%)	<5 year	13 (48.1)	16(57.1)	29(52.7)	0.60
	5-8 year	8(29.6)	6(21.4)	14(25.5)	
	>8 year	6(22.2)	6(21.4)	12(21.8)	
Weight, kg median (IQR)		14 (10-25)	14(10-32)	14 (10-26)	0.71
Glasgow coma scale, median (IQR)		13 (14-15)	14 (13-15)	14 (13-15)	0.33
Gender, male n (%)		17 (63.0)	20 (71.4)	37 (67.3)	0.51
Medical disease n (%)					
Respiratory		11 (40.7)	8 (28.6)	19 (34.5)	0.43
Infection (non-pulmonary)		3 (11.1)	6(21.4)	9 (16.4)	
Cardiovascular		1 (3.7)	0 (0)	1(1.8)	
Neurologic		7 (25.9)	8 (28.6)	15(27.3)	
Renal		0 (0)	1 (3.6)	1 (1.8)	
Metabolic		4 (14.8)	0 (0)	4(7.3)	
Hematologic		1 (3.7)	2(7.1)	3(5.5)	
Surgery		0 (0)	3 (10.7)	3 (5.5)	
PRISM score, median (IQR)		5.00 (1.00-7.00)	3.00 (2.00-5.00)	4.00 (1.75-5.00)	0.31
Systolic Blood pressure, mm Hgmedian (IQR)		89 (83-108)	104 (82-115)	94 (82-111)	0.19
Diastolic Blood pressure, mm Hg median (IQR)		51(41-62)	56 (42-65)	55 (42-65)	0.42
Mean Arterial Pressure, mm Hg median (IQR)		65 (56-77)	74 (56-81)	67 (57-80)	0.33
Heart rate, per minute median (IQR)		113 (101-130)	110 (89-130)	111 (90-130)	0.28
O2 sat, median(IQR)		98 (95-99)	98 (97-99)	98 (96-99)	0.53
Respiratory rate, per minute median (IQR)		40 (34-45)	30 (24-40)	27 (35-45)	0.06

PRISM (pediatric risk of mortality), O2 sat (oxygen saturation), IQR (Interquartile range)

Table-2: Comparison of clinical responses based on Ramsey sedation scale between the two study groups

Variables		Dexmedetomidine	Fentanyl	P
Ramsey sedation scale ≥ 3, n (%)	min 5	0 (0)	0 (0)	0.39
	min 10	9 (33.3)	4 (14.3)	
	min 15	8 (29.6)	8 (28.6)	
	min 20	6 (22.2)	6 (21.4)	
	min25	4 (14.8)	8 (28.6)	
	> min 30	0 (0.0)	2 (7.2)	
Need second dose, n (%)	Yes	24 (88.9)	26 (92.9)	0.61
Need propofol, n (%)	No	17 (63.0)	14 (50.0)	0.34
	Yes	10 (37.0)	14 (50.0)	

Table-3: Clinical data analysis per study protocol

Variables	DEX (n=17) Median (IQR)	Fentanyl (n=14) Median (IQR)	P	DEX + propofol (n=10) Median (IQR)	Fentanyl + propofol (n=14) Median (IQR)	P
Time to reach RSS≥3, median (IQR)	10.00 (10.00-15.00)	15.00 (10.00-15.00)	0.098	20.00 (20.00-25.00)	25.00 (20.00-25.00)	0.138
Procedure duration, median (IQR)	15.00 (15.00-17.50)	17.50 (15.00-20.00)	0.225	22.50 (20.00-26.25)	30.00 (23.75-30.00)	0.075

RSS (Ramsey sedation scale), IQR (Interquartile range)

Table-4: Changes in HR, RR, and MAP

Outcome	B	Std. Error	95% Wald Confidence Interval		P-value
			Lower	Upper	
HR	0.06	0.0535	-0.04	0.165	0.262
RR	0.20	0.09	-0.01	-0.38	0.035
MAP	1.47	3.43	-5.27	8.20	0.669

Table-5: Frequency of Adverse effects

Variables	DEX (n)	Fentanyl (n)	P
Apnea	0	0	-
Transient hypoxemia	3	3	0.66
need reservoir Bag mask	1	1	0.75
Bradycardia	2	0	0.26
Tachycardia	0	0	-
Hypotension	3	1	0.38
Hypertension	2	0	0.12
Bradypnea	1	1	0.74

4- DISCUSSION

Procedures requiring anesthesia in children are associated with more severe complications such as apnea and hemodynamic instability. The results of our study confirmed that the effect of DEX on sedation for CVC insertion in critically ill children is similar to fentanyl, and their side effects are comparable. Almost half of the participants in each group reached appropriate sedation, which was defined as the primary outcome. In addition, the DEX group showed numerically but not statistically faster sedation induction; indeed, DEX required a shorter procedure and did not cause any severe complication.

Similar to our results, Prasad et al. (19) found that the sedation during mechanical ventilation in the DEX group was sufficient and comparable to that in the fentanyl group, yet it was accompanied by minimal effects on hemodynamics without needing extra intervention. Mondal et al. suggested that DEX causes better sedation (i.e., higher RSS score) than fentanyl; and is associated with better hemodynamic stability (20). Likewise, Bong et al. reported adequate DEX-induced sedation, few respiratory complications, and a lower need for intubation in the case of infant patients undergoing disc herniated surgery (16).

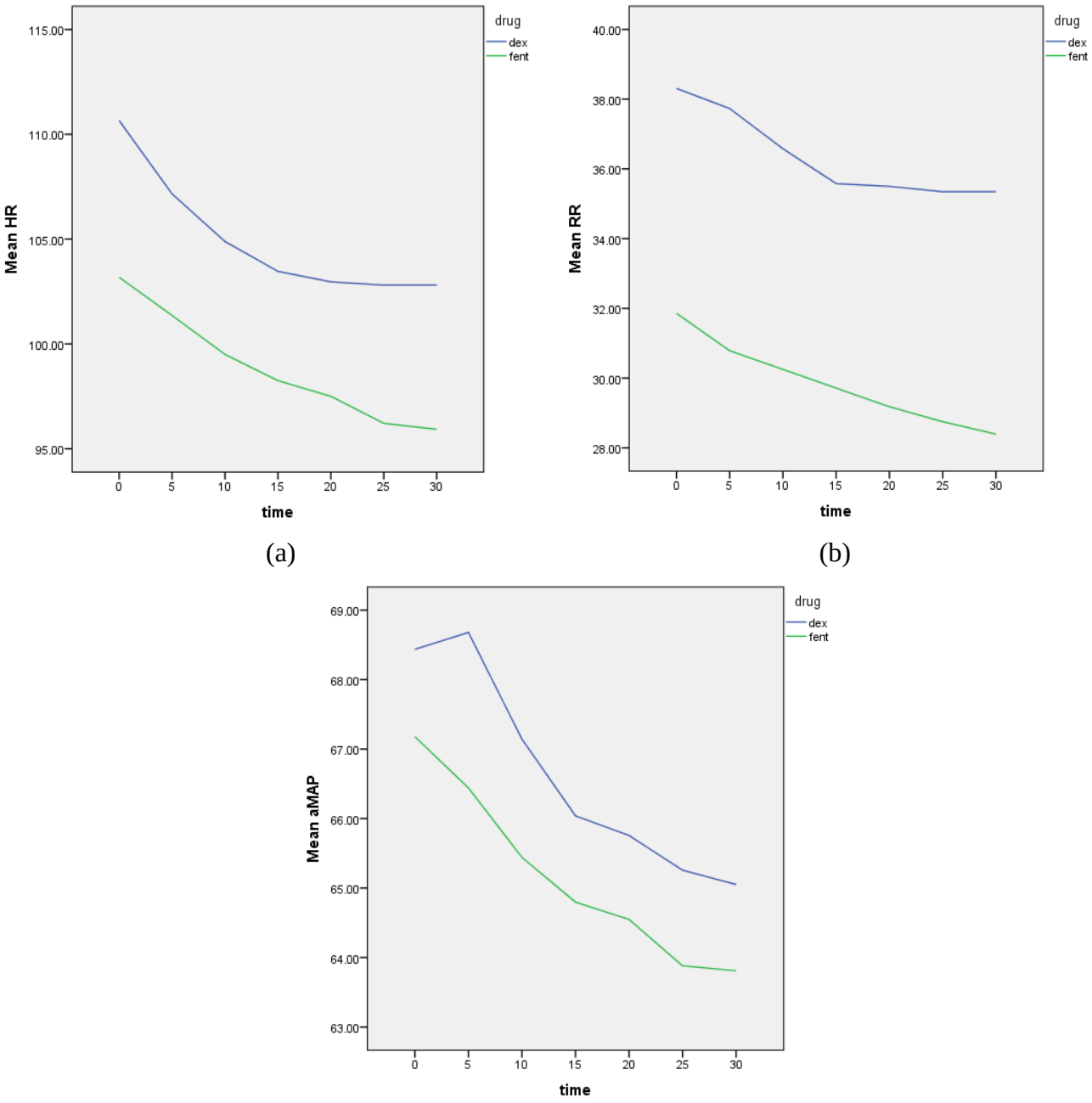

Fig. 2: Heart rate, Respiratory rate and Mean arterial pressure of Dexmedetomidine and fentanyl groups during the central venous catheter placement (time unit=minute)

Several clinical trials have suggested that combining DEX with other sedative agents could help induce the required sedation more quickly without exacerbating the adverse effects. Besides its acceptable effects, the total dosage of DEX required for patients' various sedative regimens is comparatively lower than that needed by other sedative combinations (21-23). Our findings showed the time for terminating catheterization; and reaching proper sedation was numerically faster without any side effects in the group that received the DEX and propofol combination in comparison to the group that was given the fentanyl and propofol combination;

nevertheless, the differences were not statistically significant.

In case of analgesic effects, there are some reports which compare the impact of DEX with opioids. Erdil et al. indicated that the effects of DEX and fentanyl after adenoidectomy were not different in the two groups of children (24). The same results were observed by Olutoye et al., who noted that DEX and morphine had similar effects on pain control after surgery, with DEX showing a more acceptable safety profile in terms of hemodynamic factors (25).

While the pharmacokinetic / pharmacodynamic analysis of DEX has led to the conclusion that 0.6 mic/kg as loading dose and 0.33-0.53 mic/kg per hour for maintenance dose can be adequate for most age groups of pediatric patients (26), our findings showed that even higher doses are needed to induce sufficient sedation for invasive procedures with tolerable safety profile. The effect size of DEX on HR and MAP was not significant but it was significant on RR. In other words, the mean RR in the DEX group was higher than the fentanyl group. Although the difference in RR was marginally significant between the two groups at baseline, none of the patients in the groups developed tachypnea or bradypnea based on their age. This may indicate that DEX is less likely to cause respiratory depression. This is compatible with the results obtained by Erickson et al., who stated that administering DEX for mechanically ventilated patients required higher dosing regimens (23). Another study showed that the effects of DEX at a dose of 2 mg/kg were equal to propofol, with similar cardiac complications but fewer respiratory adverse effects (27).

Studies on the safety concerns of DEX in pediatric procedures have demonstrated that this sedative is generally safe and associated with few clinically significant hemodynamic changes (17). In a study on the effect of DEX on Emergence Agitation (EA) and the quality of recovery, it was found that DEX, thanks to its fewer adverse effects compared to other drugs used to control agitation, is a better choice for EA prophylaxis in children (28). Our results confirmed that most of the adverse effects of DEX are mild to moderate and its safety profile is acceptable. Moreover, a recent systematic review and meta-analysis of studies on administering DEX for prolonged sedation in the PICU showed minimal adverse effects, even when DEX is used for more than 24 hours (29).

4-1. Limitations of the study

Our study had some limitations too. Unlike in monotherapy, the effective dose of DEX for practical sedation could not be determined by our findings. Moreover, CVC insertion is a short procedure, and therefore the effects of DEX on cardiovascular parameters were not explored in prolonged infusion time. Finally, it is not negligible that the larger the sample size, the more reliable the interpretation of the results.

5- CONCLUSION

Overall, the present study revealed that DEX is at least as safe and effective as fentanyl for CVC insertion in critically ill children. It was also found that using DEX alone or in combination with propofol is practically safe.

6- ETHICS CONSIDERATIONS

This study was approved by the Ethics Committee of Mazandaran University of Medical Sciences (IRMAZUMS.REC.1399.6381), and registered in the Iranian Registry of Clinical Trials (IRCT 20090813002342N10). This study was performed in line with the principles of the Declaration of Helsinki. The patients' families were provided with detailed explanations about the study objectives and research methods. Informed written

consents were obtained from the parents or guardians of all patients.

7- FUNDING

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8- CONFLICT OF INTEREST

None

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