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ORIGINAL PAPER

Comparison of the Effect of Intravenous Bolus Norepinephrine and Ephedrine on Prevention of Post Spinal Hypotension in Cesarean Section: a Randomized Double-Blind Clinical Trial

Nahid MANOUCHEHRIAN[a], Nasrin JEYRIAEE[b], Soma HOSEINI[b]

[a]Department of Anesthesiology, Fatemieh Medical Center, Hamadan University of Medical Sciences, Hamadan, Iran

[b]School of Medical Sciences, Hamadan University of Medical Sciences, Hamadan, Iran

ABSTRACT

Background: *Currently, cesarean section is performed under spinal anesthesia. Hypotension is the most common complication of spinal anesthesia. This study aimed to compare the effect of intravenous bolus norepinephrine and ephedrine on prevention of post spinal hypotension in cesarean section.*

Methods: *The present study was a double-blind clinical trial, in which 50 pregnant women aged 18-46 years, with ASA class I and II, were selected for cesarean section under spinal anesthesia and randomly assigned to two groups, one receiving norepinephrine (group A) and the other one ephedrine (group B). Immediately after spinal anesthesia, patients in group A received 5 µg of intravenous norepinephrine and those in group B 10 mg of intravenous ephedrine. The incidence of hypotension, bradycardia, mean systolic and diastolic blood pressure, and mean heart rate were recorded in a checklist. Patients with hypotension and bradycardia received 10 mg of ephedrine and 0.5 mg of atropine, respectively, and finally the amount of ephedrine and atropine was also recorded. Data were analyzed in SPSS, version 21 at a confidence level of 95%.*

Results: *Hypotension had a frequency of 24% and 40% (P = 0.364) and the dose of ephedrine used to treat that condition was 15.0±8.37 and 18.18±7.51 mg (P = 0.434) in the norepinephrine and ephedrine groups, respectively. The mean heart rate was significantly lower in the norepinephrine group than the ephedrine one (P <0.001).*

Conclusions: *Both norepinephrine and ephedrine were effective in preventing hypotension during cesarean section under spinal anesthesia, but tachycardia was less common with norepinephrine.*

Trial registration: *The present study was registered on 17 May 2019 in the Iranian Clinical Trial Center (https://www.irct.ir) Identifier: IRCT20120915010841N17.*

Keywords: Cesarean section, hypotension, spinal anesthesia, norepinephrine, ephedrine.

Address for correspondence:
Nahid Manouchehrian, Associate Professor
Department of Anesthesiology, Hamadan University of Medical Sciences, Fatemieh Medical Center, Pasdaran St, Hamadan, Iran
Email: manuchehryan@gmail.com

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ABBREVIATIONS

ASA: American Society of Anesthesiologists
Hypotension: Systolic blood pressure less than 90 mm Hg
Bradycardia: A heart rate less than 60 beats *per* minute

INTRODUCTION

Currently, cesarean section is performed under spinal anesthesia (1). Although spinal anesthesia has several advantages, it may cause some complications, including hypotension, bradycardia, high spinal, headache, neurological complications, etc (2). Hypotension (33%) is the most common complication of spinal anesthesia (3). Cesarean section requires a T4-T6 sensory block level; due to the high extensive sympathectomy (at the level of T1-T4), the reported incidence of hypotension in cesarean section can reach 80% of cases (4, 5).

Hypotension can cause problems for both the mother and fetus, including nausea and vomiting, dizziness, restlessness and dissatisfaction in the mother, and distress and acidosis in the fetus (6, 7). Prevention of maternal hypotension is an important factor in reducing maternal and fetal morbidity. Currently, several methods are available to prevent hypotension, including shifting the pregnant uterus to the left to avoid uterine pressure on the aortocaval, administration of crystalloids, vasopressors and reducing the dose and speed of local anesthetics (8-11). However, despite performing the above-mentioned methods, hypotension occurs during cesarean section (12). Ephedrine and phenylephrine are two vasopressors used to prevent or treat post spinal hypotension during cesarean section (13, 14). Phenylephrine has been associated with bradycardia and decreased cardiac output (13, 14). Ephedrine is a direct agonist of α and β adrenergic receptors and indirectly stimulates the release of norepinephrine from adrenergic terminals (13, 15). Ephedrine also increases myocardial oxygen consumption (15). A few studies have evaluated the effect of norepinephrine on prevention of hypotension in cesarean section that showed different results (16, 17). The present study aimed to compare the effect of intravenous bolus norepinephrine and ephedrine on prevention of post spinal hypotension in cesarean section.

METHODS

Study design

The present study was a randomized double-blind clinical trial conducted in Fatemieh Medical Center in Hamadan, Iran, between 2019 and 2020. The study population consisted of pregnant women aged 18-46 years, with ASA I and II, who were candidates for cesarean section. Data collection tools included a questionnaire to record patients' demographics and a checklist to record the consequences of cesarean section following the administration of norepinephrine and ephedrine intravenous bolus after spinal anesthesia.

Setting and participants

In the present study, pregnant women aged 18-46 years, with ASA I and II, who were candidates for cesarean section in Fatemieh Medical Center and met the inclusion criteria of the study, were consecutively selected using convenience sampling method after calculating the sample size of 50 (25 individuals per study group) based on the formula for comparing ratios in the two groups using G-power3.1 soft– ware and the relevant reference (18), and concerning the type one error, 5%, power of 80%, and effect size of 0.4. The following inclusion criteria were used: pregnant women candidates for cesarean section under spinal anesthesia, complete satisfaction to participate in the project, patients' age range 18-46 years, term pregnancy, absence of pulmonary and cardiac diseases, hypertension, diabetes, cardiac arrhythmias, and Heart failure. Exclusion criteria included failure of spinal anesthesia, emergency cesarean section, eclampsia and preeclampsia, multiple pregnancies, contraindications for spinal anesthesia (high ICP, hypovolemia, coagulation disorders, etc) and history of allergy to any of the study drugs.

Data collection

This double-blind clinical trial was performed after approval from the ethics committee of Hamadan University of Medical Sciences, Iran. In the present study, pregnant women aged 18-46 years, who were candidates for cesarean section under spinal anesthesia and met the inclusion criteria, were selected after providing oral explanations and obtaining written consent from them. Partici-

pants were then randomly allocated to two groups treated with 5 µg of norepinephrine (group A) and 10 mg of ephedrine (group B). Randomization was performed using the block randomization method. To make the study medications indistinguishable to both patients and researchers, the drugs were prepared by the anesthesia nurse in syringes of the same size and shape with A and B labels, so that the anesthesiologist would not recognize them. After entering the operating room, all patients had an 18-gauge IV catheter placed and received 10 mL/kg of Ringer serum. Then the basal systolic, diastolic, mean arterial blood pressure, heart rate, and oxygen saturation of the patients were measured using X162 monitor (Saadat Co., Iran) and recorded. Patients were first placed in a sitting position and underwent spinal anesthesia by a 25 G Quincke needle and injection of 10 mg of 0.5% bupivacaine and 2.5 µg of sufentanil into the subarachnoid space; then, they were placed in the supine position. Immediately after spinal anesthesia, patients in group A received 5 µg of intravenous norepinephrine (0.1%, 1 mg/mL, Pars Daru Co.) and those in group B 10 mg of intravenous ephedrine (ephedrine hydrochloride, 50 mg/mL, Rayan Daru Co., Iran) in similar syringes which had been prepared by an anesthesia nurse according to a pre-specified list. Afterwards, systolic, diastolic, and mean arterial blood pressure as well as heart rate were measured and recorded every two minutes up to 10 minutes, and then every five minutes up to 15 minutes, and then every 10 minutes until the end of surgery. In case of hypotension (systolic blood pressure less than 90 mm Hg and bradycardia (heart rate less than 60 beats per minute), 10 mg of ephedrine and 0.5 mg of intravenous atropine were prescribed, respectively; finally, the amount of ephedrine and atropine, incidence of bradycardia, and hypotension, nausea and vomiting, Apgar score at one minute and five minutes after birth, the presence of headache, palpitation, and post spinal shivering were also checked and recorded.

Statistical analysis

Data analysis was performed using SPSS software version 21. For descriptive statistics, tables, diagrams, frequency percentage, mean and standard deviation were used to describe and report all variables. An independent t-test was used to compare the mean of systolic and diastolic blood pressures, MAP, HR, and SpO_2 in both groups. Repeated measures analysis of variance was used to compare between different times of measurement. Moreover, ANOVA was used to compare the repeated observations and Chi-square test and Fisher's exact test for the nominal qualitative variables between the two groups. P value of less than 0.05 was considered statistically significant.

RESULTS

A total of 50 parturient women were enrolled in the present study and randomly assigned to two equal groups (25 patients per group), of which one received intravenous (IV) bolus norepinephrine and the other one IV bolus ephedrine (Figure 1).

The mean age of patients in the norepinephrine and ephedrine groups was 31.88±6.73 and 31.16±6.67 years, respectively (P = 0.706).

As shown in Table 1, there was no statistically significant difference in either the mean systolic and diastolic blood pressure at baseline and up to 60 minutes after spinal anesthesia between the two groups with norepinephrine and ephedrine (P = 0.229 & 0.644), or mean arterial pressure (MAP) at baseline and up to 60 minutes after spinal anesthesia between the two groups (P = 0.352).

According to Table 2, there was no statistically significant difference in mean pre-spinal heart rate between the two study groups. After spinal anesthesia, however, the mean heart rate was significantly lower in the norepinephrine group for up to 60 minutes compared to that in the ephedrine group (P <0.001). Also, the mean SPO_2 at minutes 25 and 30 after spinal anesthesia was significantly lower in the norepinephrine group than the ephedrine one (P <0.05), but in general, there was no significant difference between the two groups in terms of SPO_2. According to the results of repeated measures ANOVA, there was no statistically significant difference in mean SPO_2 before spinal anesthesia and up to 60 minutes after the procedure between women who had received norepinephrine and ephedrine (P = 0.211).

As shown in Table 3, there was no statistically significant difference in frequency of hypotension, bradycardia, post-spinal shivering, nausea, vomiting, headache, and palpitation between the two groups.

According to Table 4, there was no statistically significant difference in newborns' one- and five-

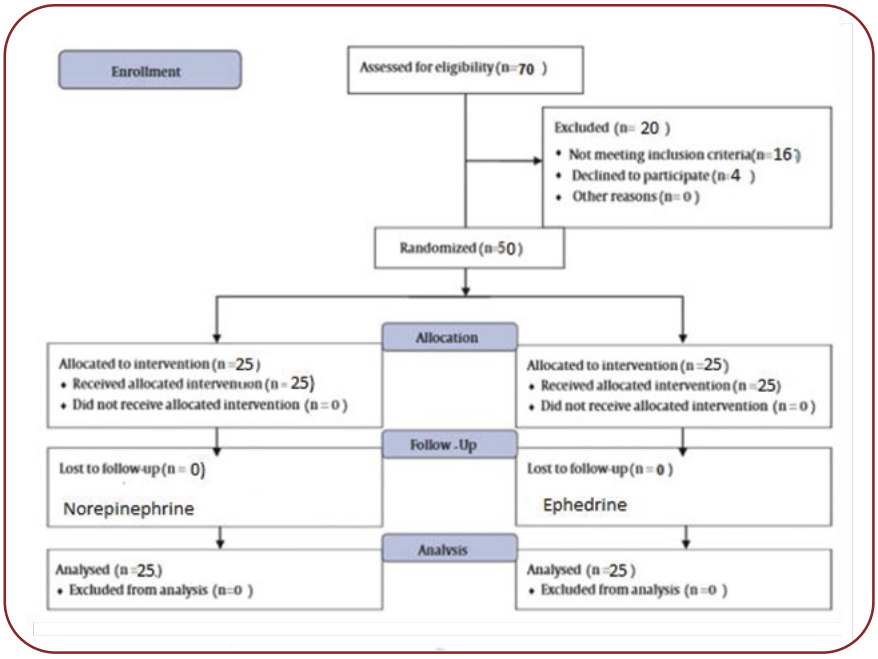

FIGURE 1. Flowchart of the trial (Consort chart)

TABLE 1. Comparison of systolic, diastolic and mean arterial pressure (MAP) in the norepinephrine (NE) and ephedrine (Eph) groups by assessment time

Assessment time	Systolic blood pressure (mm Hg)			Diastolic blood pressure (mm Hg)			MAP (mm Hg)		
	NE	Eph	P-value	NE	Eph	P-value	NE	Eph	P-value
Baseline	126.24±15.012	123.40±10.34	0.440	77.08±13.48	76.44±13.51	0.868	92.78±13.03	91.48±13.41	0.735
After spinal	123.79±17.97	121.36±13.63	0.595	72.79±15.83	74.00±14.35	0.781	89.29±17.68	87.84±14.17	0.752
After 2 min	116.32±26.47	109.84±18.81	0.323	71.76±14.26	66.28±16.67	0.218	86.96±14.66	80.04±17.59	0.137
After 4 min	107.20±20.16	103.68±19.88	0.537	60.44±15.25	61.44±15.10	0.817	75.52±14.99	75.32±15.63	0.963
After 6 min	110.16±19.78	102.12±18.43	0.144	61.88±15.78	57.28±15.62	0.306	76.92±17.37	71.08±16.26	0.226
After 8 min	108.64±15.99	105.52±20.04	0.546	59.88±11.36	59.64±13.79	0.947	77.28±12.82	73.68±14.79	0.362
After 10 min	107.56±11.79	108.52±12.03	0.777	58.20±11.15	59.08±9.56	0.766	74.20±11.50	74.76±9.51	0.852
After 15 min	109.76±17.05	108.72±9.33	0.790	57.76±12.89	59.40±10.50	0.624	74.12±14.32	73.44±9.33	0.843
After 20 min	108.12±15.85	105.48±12.68	0.519	55.84±12.79	55.40±11.62	0.899	72.08±14.28	71.12±12.03	0.798
After 25 min	105.84±13.19	104.72±10.55	0.742	55.20±10.69	54.92±10.26	0.925	72.40±10.69	71.00±10.55	0.643
After 30 min	107.68±11.58	107.84±10.55	0.959	55.92±9.20	55.72±9.96	0.942	72.40±12.14	72.04±8.86	0.905
After 40 min	108.28±11.92	107.52±8.66	0.798	56.08±8.66	56.44±8.91	0.885	72.56±10.48	72.56±7.42	1.00
After 50 min	112.28±13.52	108.44±8.05	0.228	58.28±9.84	58.16±8.16	0.963	76.64±11.19	74.08±7.66	0.350
After 60 min	112.79±14.81	109.16±8.18	0.298	60.96±10.01	59.36±7.42	0.527	77.92±12.69	75.20±6.95	0.355

TABLE 2. Comparison of mean heart rate and SPO_2 in the norepinephrine (NE) and ephedrine (Eph) groups by assessment time

Assessment time	Heart rate			SPO_2		
	NE	Eph	P-value	NE	Eph	P-value
Baseline	93.96±14.72	94.96±16.26	0.823	96.96±1.49	96.92±1.35	0.924
After spinal	84.50±18.53	98.48±14.66	0.005*	96.92±1.95	97.36±1.22	0.344
After 2 min	85.04±21.96	108.72±12.58	0.000*	97.16±1.40	97.56±1.32	0.306
After 4 min	92.60±18.36	110.12±17.33	0.001*	97.24±1.56	97.36±1.5	0.783
After 6 min	92.56±18.05	106.72±15.80	0.005*	97.00±2.27	97.32±1.57	0.565
After 8 min	95.48±18.48	106.28±12.79	0.021*	96.72±2.44	97.44±1.56	0.220
After 10 min	94.60±16.80	105.80±12.66	0.011*	96.76±2.40	97.48±1.53	0.212
After 15 min	92.68±14.36	106.24±1381	0.001*	96.52±2.26	97.56±1.44	0.058
After 20 min	93.80±14.27	106.64±10.15	0.001*	96.44±2.29	97.44±1.56	0.077
After 25 min	92.76±14.08	106.92±10.59	0.000*	96.36±2.53	97.60±1.41	0.038*
After 30 min	92.80±12.12	104.76±11.24	0.001*	96.28±2.51	97.68±1.38	0.019*
After 40 min	90.44±11.68	102.08±9.14	0.000*	97.08±2.12	97.56±1.53	0.371
After 50 min	91.08±11.32	101.52±8.82	0.001*	97.08±2.08	97.56±1.53	0.365
After 60 min	88.75±11.78	92.12±7.38	0.001*	97.04±2.03	97.72±1.37	0.180

*Significant

TABLE 3. Frequency distribution of hypotension, bradycardia and other complications in the norepinephrine (NE) and ephedrine (Eph) groups

Complications	Therapeutic group		P-value
	NE No. (%)	Eph No. (%)	
Hypotension			
Yes	6 (24)	10 (40)	0.364
No	19 (76)	15 (60)	
Bradycardia			
Yes	0 (0)	0 (0)	-
No	25 (100)	25 (100)	
Nausea & vomiting			
Yes	5 (20)	9 (37.5)	0.217
No	20 (80)	15 (62.5)	
Shivering			
Yes	3 (12.5)	3 (13)	1.000
No	21 (87.5)	20 (87)	
Headache			
Yes	2 (8)	3 (12.5)	0.667
No	23 (92)	21 (87.5)	
Palpitation			
Yes	1 (4)	0 (0)	1.00
No	24 (96)	25 (100)	

TABLE 4. Comparison of mean Apgar score and dosage of ephedrine in the norepinephrine (NE) and ephedrine (Eph) groups

Variables	Therapeutic group		P-value
	NE No. (%)	Eph No. (%)	
Dosage of ephedrine (mg)	15.±8.37	18.18±7.51	0.434
Apgar score (one minute)	8.52±0.96	8.8±0.41	0.190
Apgar score (five minutes)	9.64±0.70	9.80±0.41	0.328

minute Apgar score between the groups with norepinephrine and ephedrine. In total, one case in the norepinephrine group required atropine administration, while six patients in the norepinephrine group and 11 patients in the ephedrine group needed ephedrine supplementation to treat hypotension (P = 0.433).

DISCUSSION

In the present study, the mean heart rate up to 60 minutes after spinal anesthesia was significantly lower in the norepinephrine group than the ephedrine one. However, the two groups were not significantly different in terms of frequency of hypotension, bradycardia, mean systolic and diastolic blood pressure, mean arterial pressure, SPO_2, neonatal one- and five-minute Apgar score, nausea, vomiting, shivering, headache, and palpitation. Moreover, there was no statistically significant difference in ephedrine dose between the two groups receiving norepinephrine and ephedrine.

In a clinical trial conducted by Huang *et al* (16) to compare the effect of norepinephrine (n = 45) and ephedrine (n = 40) on the prevention of hypotension in women undergoing cesarean section under spinal anesthesia, the authors found no statistically significant difference between the ephedrine and norepinephrine groups in terms of heart rate, systolic and diastolic blood pressure, SPO_2, and one- and five-minute Apgar score (16). In line with their results, our findings showed no statistically significant difference in maternal blood pressure changes and neonatal one- and five-minute Apgar score. However, the heart rate of women in the norepinephrine group was significantly lower than that of patients in the ephedrine group. In a double-blind clinical trial conducted by Xu *et al* (17) on the prophylactic effect of norepinephrine (4 μg/min) and ephedrine on the prevention of hypotension in women undergoing elective cesarean section under spinal anesthesia, a total of 97 patients were compared in the two groups of norepinephrine (n = 48) and ephedrine (n = 49). Their results showed that the frequency of tachycardia, mean heart rate, and systolic blood pressure in the norepinephrine group was significantly lower than the ephedrine one. However, there was no significant difference in other maternal and neonatal variables (Apgar score) between the two groups (17). The sample size of our study was smaller than that of Xu *et al* In the present study, a bolus dose of 5 μg norepinephrine was administered, while Xu *et al* used a dose of 4 μg/min. The results of our study for heart rate were consistent with those reported by Xu *et al*; however, there was no significant difference in systolic blood pressure between the two groups.

Wang *et al* (19) explored the effect of norepinephrine and ephedrine boluses among 166 eligible women undergoing cesarean section under spinal anesthesia, who were assigned to three groups, with each receiving norepinephrine 4 μg (n = 56), phenylephrine 50 μg (n = 55) and ephedrine 4 mg (n = 55), respectively (19). According to their results, the heart rate of subjects in the norepinephrine group was generally higher than that of subjects in the phenylephrine group but lower than that the ephedrine group. Women in the norepinephrine group also experienced lower tachycardia than those in the phenylephrine group. There was no significant difference in neonatal one- and five-minute Apgar score between the three groups (19). Although the sample size of

the present study was smaller and phenylephrine was not included, the results of the two studies are consistent. In a study by Elnabity *et al* (20), 140 patients with ASA 1 and 2 considered for cesarean section were divided into two groups receiving 10 µg of bolus norepinephrine and 10 mg of intravenous bolus ephedrine during the spinal block; the authors found that the incidence of hypotension, hypertension, bradycardia and tachycardia in the norepinephrine group was lower than the ephedrine group, but neonatal one- and five-minute Apgar score was similar in the two groups (20). In the present study, no significant difference in the incidence of hypotension and bradycardia was observed between the two groups with norepinephrine 5 µg and ephedrine 10 mg, which was in contrast with the results reported by Elnabity *et al*. This discrepancy between results may be due to the different sample sizes and norepinephrine doses used in the studies.

Sofiene *et al* (21) performed a study on 120 pregnant women aged 18-45 years, with ASA 1 and 2, who were candidates for cesarean section under spinal anesthesia. Participants were assigned to two groups: one receiving ephedrine infusion at a dose of 10 µg/kg/min and the other one receiving norepinephrine infusion at 0.1 µg/kg/min to maintain systolic blood pressure in the range of 120-180% of baseline. The results showed that norepinephrine was able to maintain patients' hemodynamics during cesarean section under spinal anesthesia with fewer side effects compared to ephedrine (21). In the current study, however, there was no statistically significant difference in post spinal shivering, nausea and vomiting, headache and palpitation between women receiving norepinephrine and ephedrine, and those in the norepinephrine group experienced lower heart rates than those in the ephedrine group. Shafei *et al* investigated 100 patients aged 40-60 years, with coronary artery disease and ASA 2 and 3, who were arthroscopic candidates, and found that the group who received 10 mg of intravenous bolus ephedrine experienced a higher frequency of tachycardia than the group with 5 µg of norepinephrine, but there were no significant differences in incidence of hypotension, hypertension, and bradycardia between the two groups (22). Despite the difference in the type of surgery and sample size between the two studies, our findings are consistent with those of Shafei *et al*'s study. Kee *et al* (23) compared the effect of 5 µg norepinephrine *versus* 100 µg of phenylephrine on women undergoing cesarean section under spinal anesthesia (23), Dong *et al* (24) compared the effect of 10 µg norepinephrine *versus* 50 µg phenylephrine in women undergoing cesarean section under spinal anesthesia (24), Chen *et al* (18) comparing the effect of norepinephrine at 5, 10 and 15 µg/kg/h with that of normal saline, and the results showed that the infusion of 5-10 µg norepinephrine was effective in reducing the incidence of hypotension without significant side effects in mothers and infants (18). The results further showed that norepinephrine was as effective as phenylephrine in preventing hypotension, while causing no harmful effects on heart rate and maintaining cardiac output at a higher level compared to phenylephrine (24). And finally, norepinephrine was much more effective in maintaining blood pressure and was associated with an increased cardiac output and heart rate compared with phenylephrine, but does not affect the neonatal outcome (23).

Limitations of the study

The main limitation of the present study is the small sample size. So, further high quality research with a larger sample size is needed to strengthen the evidence base.

CONCLUSION

Both norepinephrine and ephedrine were effective in preventing hypotension during cesarean section under spinal anesthesia, but heart rate was lower in the norepinephrine group than the ephedrine group. ❑

Avaibility of data and materials: Data that support the findings of this study are available from the corresponding author.

Conflicts of interest: none declared.

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Ethics approval and consent to participate in research: The current study was approved by the Ethics Committee of Hamadan University of Medical Sciences, Iran, on the 23rd of February 2019, with the number IR.UMSHA.REC.1397.867. It was also registered in the Iranian Registry of

Clinical Trials with the number IRCT20120915010841N17.

Written informed consent was obtained from all patients before initiation of the study.

Authors' contribution: Nahid Manouchehrian was responsible for the study concept and design, Nahid Manouchehrian, Nasrin Jeyriaee and Soma Hoseini for data analysis and interpretation, Nahid Manouchehrian for manuscript drafting, Nahid Manouchehrian for critically reviewing the manuscript for important intellectual content, Nasrin Jeyriaee for statistical analysis, Nahid Manouchehrian and Soma Hoseini for administrative, technical and material support. All authors approval the final version of the manuscript before submitting it for publication.

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