No concerns for post-stroke seizure or epilepsy with rTPA; A retrospective cohort study

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Research Article

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Abstract

Background:

Recombinant tissue plasminogen activator (rTPA) is the gold standard therapy for ischemic stroke patients within the appropriate time interval. In addition to its undoubtedly benefits, recognizing its possible adverse effects is of utmost importance. This study aims to investigate the possible correlation between rTPA administration and the risk of post-stroke epilepsy.

Methods:

In a retrospective cohort study, we enrolled subjects identified to have an ischemic stroke event without prior history of epilepsy based on their medical records. Then, followed them retrospectively regarding any subsequent seizure or epilepsy syndromes.

Results:

rTPA therapy showed no correlations with seizures during the first week after stroke or with the epilepsy syndromes. Positive history of prior ischemic stroke, cortical localization of stroke, cardio embolic source of the stroke, and positive hemorrhagic complication were predictors of post-stroke seizure during the first week following the stroke event. Higher final Modified Rankin Scale (MRS) and cortical localization of stroke were predictors of post-stroke epilepsy (PSE).

Conclusion

rTPA is a safe therapeutic measure for patients with ischemic stroke with no concerns of subsequent development of post-stroke seizure or epilepsy.

Introduction

Stroke is the leading cause of severe life-long disability and has imposed high burdens on the health care systems.[1,2] Recombinant Tissue plasminogen activator (rTPA) is the mainstay treatment for stroke patients within the appropriate time interval. These medications have been proven to be drastically effective in restoring the blood flow to ischemic areas and thus, preventing further infarction and secondary damage.[3,4].

Evidence obtained from long-term follow-ups shows that rTPA is significantly effective in decreasing post-stroke mortality rates and improves the survivor's quality of life.[5] Despite rTPA's undoubtedly benefits, multiple side effects have been reported in correlation with this agent, the most commonly

known one being hemorrhage.[6] Epileptogenic effects are also noted as one of the complications of rTPA that may damage the central nervous system.

Studies indicate that expression of endogenous tPA in mice is associated with lower seizure thresholds, secondary to upregulation of NMDA receptors.[7,8]

Post-stroke seizure (PSS) is one uncommon yet very important complication of stroke. The term is generally classified by the time of occurrence. Early PSS appears within the first seven days, whereas post-stroke epilepsy (PSE) is defined as at least two episodes of convulsion after the first week.[9]

The incidence of overall PSS is estimated to be 5–15% among various studies. The prevalence of PSE specifically is much fewer investigated[10–12]. A cohort study conducted on 1179 patients in Denmark reported that 3% of stroke patients developed PSE in a seven-year follow-up.[10] Prior research has suggested multiple predictive factors for PSE such as age, stroke severity, cortical location, and hemorrhage.[11]

Recently, some clinical studies have suggested an association between the administration of rTPA and PSS. These seizures are known as one of the main factors that negatively affect patient's quality of life. This possible correlation would lead to a serious clinical dilemma for using rTPA. Hence, it is necessary to further elucidate PSE incidence, its predictive factors, and the high-risk patients to consider other treatment options such as mechanical thrombectomy for these patients. [8,13,14]. This study investigates the possible correlation between rTPA therapy and PSS with consideration of various clinical and paraclinical factors.

Methods

In a retrospective cohort study, we assessed the correlation between receiving rTPA in ischemic stroke patients and the development of early PSS (during the first week following the ischemic event) or development of PSE (after the first week). We used electronic medical records from three university hospitals located in Tehran, Iran, to ascertain the contact information of patients who were eligible to be enrolled. Eligibility criteria for this assessment included ischemic stroke patients regardless of their history of seizure events and excluded those patients with prior history of epilepsy or antiepileptics medications use. Patients were called and asked about any incidence of seizure attacks during or after the first week, demographic (age and sex), and clinical parameters (Hypertension, mRS, medication history of statins). Subjects consented verbally on the phone call to participate in the study by allowing the researchers to use their verbally expressed data and their previously recorded hospital information. Hospital health records including systolic BP on admission, BS on admission, Na level on admission, Total cholesterol on admission, National Institute of Health Stroke Scale (NIHSS) score, mRS before the stroke event, history of prior ischemic stroke, stroke localization, TOAST classification (Trial of Org in Acute Stroke Treatment) of their ischemic event, hemorrhagic complications, atrial fibrillation, ejection

fraction on the time of hospitalization. Data were anonymized on the final dataset to conserve patients' personal and clinical information confidentiality.

Statistical methods:

Description of the qualitative data was performed by frequencies, while quantitative data were described by means and standard deviations or median and interquartile ranges, based on the normality of the statistics. Logistic regression with control on accompanying parameters was handled to assess correlations between rTPA and seizure and epilepsy; adjusted relative risks are reported. Parametric data were compared using the student T-test and Mann-Whitney U Test. A P-value equal to or less than 0.05 was considered statistically significant. Stratified analysis was performed to assess possible confounders or effect modification from baseline parameters. Analyzes were performed using IBM SPSS version 22.

Results

Nine-hundred and fifty-five cases were eligible and consented to participate in this study, among which 176 had received rTPA while 779 had not. The seizure was positive in 33 patients during the first week after stroke and epilepsy was positive in 60 patients.

History of rTPA therapy showed no significant correlation with the incidence of early PSS (P-value: 0.101; Chi-square; Adjusted RR: 17.84 [0.56–559.8]); [Table 1]. rTPA therapy was not also associated with development of subsequent epilepsy syndromes in ischemic stroke patients (P-value: 0.743; adjusted RR: 0.65 [0.54–8.04]); [Table 1]. Types of seizure or epilepsy are also described by their frequencies in Table 1.

Table 1
Correlation between rTPA and seizure events and description of seizure type

Parameter (N; Mean ± SD)		Seizure 1st week post stroke		P-value [a] Adjusted RR [CI]	Seizure after the 1st week post stroke		P-value [a] Adjusted RR [CI]
		Positive (33) 4%	Negative (845) 96%		Positive (60) 7%	Negative (791) 93%	
rTPA	P	8 (1%)	164 (19%)	0.101 [a] 17.84 [0.56 – 559.8]	13 (1.5%)	155 (18%)	0.743 [a] 0.65 [0.54– 8.04]
	N	25 (3%)	681 (77%)		47 (5.5%)	636 (75%)	
Seizure type (r-TPA/Non-r-TPA)	Focal aware	1/2			1/1		
	Focal unaware	2/2			2/4		
	Focal to generalized	0/1			2/1		
	GTC	2/10			6/30		
	Myoclonic aware	0/1			0/2		
	Unknown	2/10			1/10		

P: Positive; N: Negative; CI: Confidence Interval; GTC: Generalized Tonic Colonic; a: Chi-square test

Baseline parameters including age (P-value: 0.425), history of hypertension (P-value: 0.981), BS on admission (P-value: 0.406), Na level on admission (P-value: 0.076), improvement in MRS(P-value: 0.531), and EF categories (P-value: 0.981) were not statistically significantly different between subjects with or without prior history of rTPA therapy [Table 2]. None of these parameters showed effect modification on neither early PSS nor PSE by stratified analysis.

Table 2
Descriptive statistics of demographic and clinical parameters and baseline equity assessment

Parameter (Mean ± SD; Median (IQR))		rTPA		P-value (Test)
		Positive (176)	Negative (779)	
Age		66.32 ± 13.01	67.23 ± 13.62	0.425 [a]
Sex	F	53	313	0.013 [b]
	M	123	466	
HTN	P	119	522	0.981 [b]
	N	57	249	
Statins	P	147	558	0.008 [b]
	N	29	196	
BS on admission		133.00 (48)	132.00 (76)	0.406 [c]
Na level on admission		139.45 ± 3.62	140.21 ± 5.34	0.076 [a]
Total cholesterol on admission		182.48 ± 42.59	162.46 ± 45.04	< 0.001 [a]
NIHSS	Minor	16	113	< 0.001 [b]
	Moderate	118	228	
	Moderate to severe	19	45	
	Severe	2	12	
mRS improvement		0.77 ± 2.79	0.93 ± 2.58	0.531 [a]
Prior ischemic stroke	P	38	245	0.010 [b]
	N	132	510	
Stroke localization	Cortical	90	307	0.003 [b]
	Subcortical	49	310	
	Lacunar	33	116	
	Other	1	20	
TOAST	Cardioembolic	68	229	0.001 [b]
	Lacunar	25	184	
	Large artery disease	24	71	

Parameter (Mean ± SD; Median (IQR))		rTPA		P-value (Test)
		Positive (176)	Negative (779)	
	Other	17	50	
	Undetermined	35	227	
Hemorrhagic complications	P	18	26	< 0.001 b
	N	90	466	
Atrial fibrillation	P	35	114	< 0.001 b
	N	81	601	
EF categories	> 30	141	622	0.381 b
	< 29	13	43	
DM: Diabetes Mellitus; HTN: Hypertension; P: Positive; N: Negative; F: Female; M: Male; a: T-test; b: chi-square test; c: Mann-Whitney U test				

Sex, medication history of statins, total cholesterol on admission, NIHSS categories (**NIHSS scoring**: 1–4: minor stroke; 5–15: moderate stroke; 15–20: moderate to severe stroke; 21–42: severe stroke), history of prior ischemic stroke, Stroke localization, TOAST classification, Hemorrhagic complications, and atrial fibrillation were statistically significantly different between cases with and without rTPA therapy (P-values < 0.05) [Table 2]. None of these parameters showed a confounding effect by stratified analysis, and again we found no significant correlation between rTPA therapy and seizure or epilepsy events across different categories of the mentioned parameters [Table 3].

Table 3
Stratified analysis of effect of demographic and clinical parameters on the association between rTPA and seizure events during and after the 1st week following stroke

Parameter (OR [CI] /P-value)		Correlation between rTPA and seizure during the 1st week post stroke	Correlation between rTPA and seizure after the 1st week post stroke
Age	=< 55	4.28 [0.63–29.12] / 0.162 [a]	1.42 [0.41–4.89] / 0.699 [a]
	[55–74]	1.25 [0.41–3.78] / 0.754 [a]	1.25 [0.58–2.70] / 0.559 [b]
	=>75	0.85 [0.19–3.73] / 1.000 [a]	0.64 [0.15–2.74] / 0.744 [a]
Sex	F	1.40 [0.30–6.42] / 0.651 [a]	1.43 [0.61–3.34] / 0.418 [a]
	M	1.23 [0.49–3.05] / 0.656 [b]	1.01 [0.44–2.29] / 0.977 [b]
HTN	P	1.51 [0.65–3.51] / 0.336 [b]	1.32 [0.66–2.62] / 0.422 [b]
	N	0.80 [0.09–6.77] / 1.000 [a]	0.74 [0.22–2.44] / 0.773 [a]
Statins	P	1.47 [0.66–3.27] / 0.340 [b]	0.93 [0.48–1.82] / 0.847 [b]
	N	N/A / 1.000 [a]	3.89 [0.92–16.38] / 0.084 [a]
BS on admission	< 200	0.98 [0.37–2.57] / 0.976 [b]	1.21 [0.61–2.40] / 0.578 [b]
	201–400	3.09 [0.54–17.41] / 0.215 [a]	0.52 [0.07–3.91] / 1.000 [a]
	> 401	2.42 [0.23–24.97] / 0.434 [a]	1.61 [0.36–7.13] / 0.61 [a]
Na level on admission	Normal	1.50 [0.68–3.31] / 0.310 [b]	1.25 [0.67–2.33] / 0.482 [b]
	Abnormal	N/A / 1.000 [a]	0.50 [0.06–3.75] / 0.678 [a]
Total cholesterol on admission	Normal	1.12 [0.31–3.95] / 0.742 [a]	1.13 [0.53–2.41] / 0.737 [b]
	Abnormal	1.45 [0.54–3.89] / 0.550 [a]	1.10 [0.42–2.85] / 0.791 [a]
NIHSS	Minor	N/A / 1.000 [a]	1.80 [0.41–7.92] / 0.356 [a]
	Moderate	1.38 [0.57–3.34] / 0.469 [b]	1.14 [0.42–3.05] / 0.793 [b]
	Moderate to severe	N/A / 0.548 [a]	1.83 [0.28–11.94] / 0.607 [a]
	Severe	N/A / 1.000 [a]	N/A / 1.000 [a]
Prior ischemic stroke	P	1.39 [0.41–4.67] / 0.482 [a]	1.36 [0.48–3.84] / 0.524 [a]
	N	1.60 [0.56–4.53] / 0.365 [a]	0.97 [0.45–2.07] / 0.944 [b]

Parameter (OR [CI] /P-value)		Correlation between rTPA and seizure during the 1st week post stroke	Correlation between rTPA and seizure after the 1st week post stroke
Stroke localization	Cortical	1.50 [0.67–3.36] / 0.323 [b]	1.08 [0.52–2.22] / 0.829 [b]
	Subcortical	N/A / 1.000 [a]	0.80 [0.19–3.44] / 1.000 [a]
	Lacunar	N/A / 1.000 [a]	0.68 [0.08–5.62] / 1.000 [a]
	Other	N/A / 1.000 [a]	N/A / 1.000 [a]
TOAST	Cardioembolic	1.94 [0.79–4.73] / 0.160 [a]	1.29 [0.52–3.21] / 0.595 [a]
	Lacunar	N/A / 0.595 [a]	1.23 [0.38–3.98] / 0.720 [a]
	Large artery disease	N/A	0.56 [0.07–4.58] / 1.000 [a]
	Other	N/A	N/A / 1.000 [a]
	Undetermined	1.03 [0.12–8.32] / 1.000 [a]	1.75 [0.51–5.95] / 0.411 [a]
Hemorrhagic complications	P	1.38 [0.31–6.10] / 0.683 [a]	1.91 [0.35–10.27] / 0.638 [a]
	N	0.55 [0.13–2.36] / 0.550 [s]	1.02 [0.49–2.11] / 0.955 [b]
Atrial fibrillation	P	2.27 [0.53–9.64] / 0.365 [a]	0.60 [0.14–2.62] / 0.729 [a]
	N	1.20 [0.36–4.01] / 0.732 [a]	1.66 [0.79–3.48] / 0.176 [b]
EF categories	> 30	1.01 [0.38–2.66] / 1.000 [a]	1.28 [0.68–2.38] / 0.438 [b]
	< 29	6.83 [0.67–69.02] / 0.125 [a]	N/A / 1.000 [a]

DM: Diabetes Mellitus; HTN: Hypertension; P: Positive; N: Negative; F: Female; M: Male; a: Fischer exact test; b: chi-square test; N/A: Not Applicable

NIHSS scoring: 1–4: minor stroke; 5–15: moderate stroke; 15–20: moderate to severe stroke; 21–42: severe stroke

A higher rate of PSE was associated with a higher MRS(P-value: 0.007; T-test). Positive prior history of ischemic stroke was associated with higher seizure rates during the first week after stroke (P-value 0.019; Chi-square test; RR: 2.21 [1.12–4.35]). A higher rate of cortical localization of stroke was associated with a higher rate of early PSS (P-value: 0.002; Chi-square). Cortical localization was also associated with a higher rate of PSE (P-value: 0.049; Chi-square). In the TOAST classification, the cardioembolic source of the stroke, was associated with a higher rate of early PSS (P-value: 0.013; Chi-square). Post-stroke hemorrhagic complications were associated with higher rates of early PSS (P-value: 0.009; Chi-square;

RR: 3.78 [1.59–8.98]). Other parameters were not correlated to post-stroke early seizure or post-stroke epilepsy (P-values > 0.05) [Table 4].

Table 4
Descriptive statistics of demographic and clinical parameters

Parameter (Mean ± SD; Median (IQR))		Seizure during the 1st week post stroke		P-value (Test)	Seizure after the 1st week post stroke		P-value (Test)
		Positive	Negative		Positive	Negative	
Age		69.68 ± 11.06	66.56 ± 13.51	0.205 [a]	65.00 ± 11.67	66.82 ± 13.40	0.310 [a]
Sex	F	10	321	0.371 [b]	29	290	0.072 [b]
	M	23	524		31	501	
HTN	P	26	566	0.096 [b]	41	541	0.970 [b]
	N	6	276		19	248	
Statins	P	28	647	0.206 [b]	50	624	0.165 [b]
	N	4	181		7	154	
Systolic BP on admission		150.45 ± 27.0	149.59 ± 28.18	0.873 [a]	147.22 ± 25.94	149.32 ± 27.52	0.615 [a]
BS on admission		142.00 (53)	132.00 (70)	0.092 [d]	136.50 (78)	132.00 (66)	0.341 [d]
Na level on admission		140.00 (5)	140.00 (4)	0.771 [d]	139.00 (5)	140.00 (4)	0.052 [d]
Total cholesterol on admission		179.00 (101)	162.00 (60)	0.109 [d]	169.67 ± 49.41	166.64 ± 45.35	0.658 [a]
NIHSS	Minor	4	116	0.670 [b]	9	108	0.227 [b]
	Moderate	19	312		16	309	
	Moderate to severe	2	55		4	47	
	Severe	1	12		2	9	
Current mRS score		3.43 ± 2.20	2.65 ± 2.21	0.058 [a]	3.33 ± 2.05	2.53 ± 2.16	0.007 [a]
Prior ischemic stroke	P	16	252	0.019 [b]; RR: 2.21 [1.12–4.35]	21	238	0.379 [b]
	N	16	577		37	538	
Stroke localization	Cortical	25	348	0.002 [b]	35	320	0.049 [b]
	Subcortical	5	310		16	297	

Parameter (Mean ± SD; Median (IQR))		Seizure during the 1st week post stroke		P-value (Test)	Seizure after the 1st week post stroke		P-value (Test)
		Positive	Negative		Positive	Negative	
	Lacunar	2	143		6	135	
	Other	1	20		2	19	
TOAST	Cardioembolic	19	267	0.013 [b]	21	255	0.383 [b]
	Lacunar	7	171		17	152	
	Large artery disease	0	93		6	82	
	Other	0	55		2	59	
	Undetermined	7	238		14	224	
Hemorrhagic complications	P	6	37	0.009 [c]; RR: 3.78 [1.59–8.98]	5	36	0.401 [c]
	N	19	497		45	470	
Atrial fibrillation	P	7	130	0.304 [c]	12	121	0.323 [b]
	N	20	606		40	566	
EF categories	> 30	25	674	0.439 [c]	50	632	0.565 [c]
	< 29	3	50		3	43	

DM: Diabetes Mellitus; HTN: Hypertension; P: Positive; N: Negative; F: Female; M: Male; a: T-test; b: chi-square test; c: Fischer-exact test; d: Mann-Whitney U test

Discussion

There are conflicting data about the risk of early PSS in patients with ischemic stroke undergoing treatment with rTPA. However, our analysis does not support the existence of a strong positive association between reperfusion therapies and PSS. In this study, the proportion of patients with early PSS following reperfusion therapies was 8 patients out of 176 patients and it showed no significant correlation with the incidence of post-stroke seizure during the first week following the stroke event. rTPA therapy was not also associated with the development of subsequent epilepsy syndromes in ischemic stroke patients happening in 13 patients out of 176. which is even less than the overall risk of acute symptomatic seizures after an ischemic stroke.

Various studies have been done on this scope. Data on PSE are somewhat in contrast with data on early PSS and notably, no study found that rTPA was an independent predictor of PSE. However, the role of rTPA in favoring early PSS is still under debate, and recent studies produced different results. A meta-

analysis showed that intravenous thrombolysis was not associated with early seizures after cerebral ischemia [15]. A similar finding was observed in another study where they found a nonsignificant trend toward an even lower incidence of seizure in patients treated with rTPA, particularly late seizures [16]. However, in a retrospective study by Alveraz et al. a higher risk of PSS with rTPA was observed [17], and Brigo et al. found that rTPA was associated with a doubled risk for early PSS [14].

Regarding age at stroke onset, we found no association between age and neither early PSS nor PSE. However, the association between young age and PSE has been observed. In general, registry-based study patients aged 85 years or over were about 10 times less likely to develop PSE as compared with those aged 65 years or less [18]. Other 2 retrospective studies also documented an association between younger age at onset and seizures [19], [20].

We confirmed the favoring role of cortical lesions in the occurrence of both early PSS and PSE. The cardioembolic source of the stroke, which is associated with more cortical lesions, is related to higher rates of PSS. Many studies support the epileptogenic role of cortical involvement, and they confirm that cortical involvement is associated with a higher risk of seizure [15],[21],[22]. About the role of ICH, an extra vasal blood in cerebral parenchyma has been known to be epileptogenic for many years, both in animal models of hemorrhage [23] and in patients [15]. The results of the present study confirm its role in inducing early PSS. By contrast, some studies failed to find hemorrhage as a predictor of PSE [14], [24].

Regarding stroke etiology, most post seizures occurred due to cardiac embolism, confirming that it could accelerate the risk of acute symptomatic seizures following stroke, as previously reported [25],[26]

Generalized convulsive seizures were the most frequent seizure type in this study, with no case of nonconvulsive seizure or status epilepticus recorded. Focal unaware seizures were the second seizure type recognized in this study, while it is the most common seizure type in other studies. The low frequency of focal unaware and nonconvulsive seizures could be due to the retrospective nature of the study, with the risk of underrecognition due to the lack of systematic video-EEG recording, which is necessary to reliably assess the incidence of early PSS in patients with stroke, which otherwise can be clinically underestimated [27]. In addition, patients experiencing nonconvulsive seizures or focal unaware may have difficulties recalling and accurately describing the symptoms. Moreover, detecting these seizures by caregivers can be challenging since the impairment of consciousness can be a common expression of the stroke itself in the first post-stroke days. The clinical manifestations of seizures can be so subtle that the undergoing epileptic activity is not adequately recognized. This is especially the case in elderly patients, in whom focal seizures present differently than in younger adults [28].

Seizure after stroke has been associated with higher risks of disability and mortality [29–31]. Alvarez et al. found that rTPA-treated patients with early PSS have a less favorable 3-months functional outcome [17]. In Gensicke et al.'s study, seizures were independent predictors of poor long-term outcomes in rTPA-treated patients [32]. In our study, a higher rate of PSE was associated with a higher MRS.

It has been said that a higher cholesterol level is protective from seizures [12], [33]. For instance, cholesterol-derived medications like neurosteroids have anticonvulsant activities [34]. However, our data do not support the protective effect of hypercholesterolemia or pre-stroke statin use against acute seizure, probably due to its marginal effect and a limited number of cases.

We found no significant correlation between rTPA therapy and seizure or epilepsy events across different categories of sex, medication histories of statins, anticoagulants, total cholesterol on admission, NIHSS categories, history of prior ischemic stroke, Stroke localization, TOAST classification, Hemorrhagic complications, and atrial fibrillation. Although there was a statistically significant difference through these factors between cases with and without rTPA therapy, none of these items showed a confounding effect by stratified analysis, and no significant association between rTPA therapy and early PSS and PSE was found across different categories mentioned above.

When choosing a diagnostic or therapeutic approach, we should always consider the ones with higher precision and lower possibility of adverse effects, for instance, in diagnosing extracranial stenosis, ultrasonography could serve as a precise and non-invasive diagnostic modality in place of digital subtraction angiography [35].

In summary, patients treated with rTPA had the same frequency of epileptic manifestations as non-treated patients. However, the functional outcome of patients with PSS was poorer.

Conclusion

rTPA is a safe therapeutic measure for patients with ischemic stroke with no concerns of subsequent post-stroke seizure or epilepsy development. Early PSS was associated with a positive history of prior ischemic stroke, cortical localization of stroke, cardio embolic source of the stroke, and hemorrhagic complication. PSE was associated with higher final mRS and cortical localization of stroke.

Declarations

Declarations of interest: None

Ethics approval and consent to participate:

All methods and experimental protocols were carried out in accordance with relevant guidelines and regulations, also the study is approved by Ethics Committee of Vice Chancellor for the Iran University of Medical Sciences (IUMS) by code number: IR.IUMS.REC.1399.499. All subjects were consented on the phone call to use their information which was obtained through both call and their previously recorded hospital information, and Verbal (via phone call) informed consent was obtained from all patients. This form of informed consent was approved by the Iran University of Medical Sciences, Research Ethics Committee.

Consent for publication

Verbal (via phone call) informed consent was obtained from all patients to use their health data for this publication and this form of informed consent was approved by the Iran University of Medical Sciences, Research Ethics Committee.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest/Competing interests

Authors declare no financial or non-financial conflict of interest in subject matters of this article.

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Authors' contributions:

All authors have read and approved the manuscript. Mohammad Hossein Abbasi: conceptualization, data monitoring, data analysis, writing-original draft, review &editing. Sara Esmaeili: Conceptualization, methodology, writing original draft. Seyedeh Narges Tabatabaee: writing-original draft, review &editing. Mahdi Saberi Pirouz: data collection, writing original draft. Mohammad Taghi Joghataei: supervision, review & editing. Mahisa Mokhtari: Data collection, initial drafting, supervision. Seyedeh Niloufar Rafiei Alavi: Data collection, initial drafting. Keihan Mostafavi: Data collection & monitoring. Samaneh Tanhapour Khotbehsara: Data collection & monitoring. Fateme Siahpoosh: Data collection & monitoring. Sevim Soleimani: Data collection & monitoring. Jaber Hatam: Data collection & monitoring. Zahra Mirzaasgari: conceptualization, data monitoring, methodology, supervision, review & editing

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