ORIGINAL ARTICLE

The Effects of Nebivolol on Moderate Traumatic Brain Injury in a Rat Model: Implications for Pediatric Neuroprotection

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ABSTRACT

Objectives: Traumatic Brain Injury (TBI) is a significant public health problem. Nuclear factor E2-related factor 2 (Nrf2) is a transcription factor regulating oxidative stress and inflammation after TBI. This study examined the neuroprotective potential of Nebivolol in a rat model of moderate TBI, with a focus on implications for pediatric therapy.
Materials & Methods: Twenty-one male Wistar rats (230 ± 10 g) were included. The animals were trained using the Morris Water Maze (MWM) test, and mTBI was induced using a pendulum-based method. Nebivolol was administered at a dose of 0.05 mg/kg daily from day 8 to day 21 post-injury. Behavioral assessments were performed using the MWM, while structural brain changes were evaluated via micro-computed tomography (micro-CT). Inflammatory biomarkers were also analyzed.
Results: The results revealed significant post-TBI increases in inflammatory markers (CRP, cortisol) and decreases in prolactin levels in control animals ($p<0.01$). Nebivolol treatment attenuated these biochemical changes while maintaining cardiovascular stability. The MWM demonstrated improved late-phase cognitive recovery in Nebivolol-treated subjects despite initial learning impairment. Nebivolol treatment significantly attenuated these biochemical changes. While early learning in the MWM was impaired, animals treated with Nebivolol established superior late-phase cognitive recovery. It suggests enhanced neuroplasticity. Nebivolol also maintained cardiovascular stability without inducing bradycardia.
Conclusion: The results demonstrated that Nebivolol treatment significantly modulates TBI-induced physiological changes, such as CRP and cortisol, while maintaining cardiovascular stability. Although it showed protective effects against TBI-related stress responses, the observed neuroendocrine alterations suggest complex systemic interactions. Nebivolol reduces inflammation, stabilizes cardiovascular function, and finally promotes cognitive rehab. The pleiotropic profile of Nebivolol promises reliable research in pediatric-focused models and forthcoming clinical trials.

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Introduction

Traumatic Brain Injury (TBI) is a significant global public health challenge and a leading cause of acquired disability and mortality in the pediatric population (1). The immature brain is uniquely vulnerable to trauma, and moderate-to-severe TBI in children can lead to lifelong deficits in cognition, behavior, and academic achievement, disrupting critical windows of neurodevelopment (2). Dysregulated inflammation and oxidative stress, as a booster of functional deficits and

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neuronal damage, play a central role in this pathophysiology, which can persist for weeks to months after the initial insult (3).

The Nuclear factor E2-related factor 2 (Nrf2) pathway serves as a master regulator of cellular defense mechanisms against inflammation and oxidative stress. Activating this pathway is essential for reducing oxidative damage and inflammation, making it a promising therapeutic target for safeguarding the developing brain following TBI (4).

Rat models are required for translational TBI research, including pediatric TBI, as they model critical pathophysiological features of human injury, such as blood-brain barrier disruption, cognitive deficits, and neuroinflammation (5). Inducing moderate TBI with the pendulum-impact procedure provides controlled, reproducible robotic force to the closed skull, resulting in diffuse axonal injury and neuroinflammation that mimics clinical moderate TBI (6, 7). This model reliably delivers quantifiable mental impairment and biomarker changes, presenting a validated platform for assessing neuroprotective interventions (5, 8).

Nebivolol is a third-generation β11-β11-adrenergic receptor antagonist. It displays amazing pleiotropic effects beyond cardiovascular modulation. Nebivolol enhances nitric oxide (NO) bioavailability, promotes endothelial nitric oxide synthase (eNOS) activity, and confers vasodilatory, anti-inflammatory, and antioxidant effects (9, 10). These properties– potentially linked to Nrf2 pathway activation– suggest Nebivolol may simultaneously target multiple secondary injury mechanisms in TBI (١1). Furthermore, its favorable hemodynamic profile is a significant advantage when considering treatment for children, where hypotension must be avoided.

While beta-blockers have been explored in TBI for attenuating catecholamine-mediated hypermetabolism, their application in the context of the developing brain remains limited. The distinct effects of Nebivolol on inflammation, oxidative stress, and neuroendocrine responses in moderate TBI in a model relevant to pediatric populations remain poorly characterized. This study, therefore, aimed to investigate the impact of Nebivolol on cognitive recovery (Morris water maze), structural brain integrity (micro-CT), and inflammatory/neuroendocrine biomarkers (CRP, cortisol, prolactin) in a validated rat model of moderate TBI, with a specific focus on interpreting findings for their potential translational value in pediatric neuroprotection.

Materials & Methods

Animal study

This study utilized a well-established rodent model of diffuse TBI, which recapitulates key aspects of pediatric concussion and moderate TBI, including axonal injury and neuroinflammation [6, 7]. In this study, 21 male Wistar rats weighing 230 ± 10 grams were acclimated for one week in a lab environment with a 12-hour light/dark cycle and a temperature of 22 ± 2 °C. All procedures followed international guidelines for the care and use of laboratory animals.

Three groups, including the control, Sham, and treatment groups, were assessed, and m-TBI was evaluated in the Nebivolol treatment group using the pendulum. Rats were anesthetized by the peritoneal method with acepromazine at 2 mg/kg and ketamine at 50 mg/kg. Heads were sterilized and shaved with 73% alcohol and 10% iodine. This study generated shear wounds using 20 scalpels, each 4 cm long, following ethical principles. The device was used with 15 Newton's force, and the control group and treatment group suffered concussions (12). The researchers recovered the rats and placed each in its designated cage. This research built a pendulum (weight: 10 kg) with a length of 40 cm, and the launch height was measured and controlled by a gauge with a radius of 34 cm. Due to the pendulum's specific weight and the launch's variable height, we can achieve the desired newness. It crashed with the fixed piston after hitting the pendulum unrepeatably and momentarily. The subsequent force was shifted to the second piston, which was alleviated on the mouse's head by a pneumatic tube (13). The Nebivolol group received Nebivolol tablets for two weeks, and the control group received a placebo (normal saline).

Biochemical and clinical tests

Prolactin and cortisol were used to assess the severity of inflammation in TBI. The main inflammatory markers in TBI include CRP, prolactin, cortisol, and ESR. These factors can display drug special effects at the biochemical and molecular levels.

The current study assessed the samples with a micro-CT device in the laboratory to confirm the presence of a moderate concussion before any intervention. This study scanned rats with a microcytic device and assessed the subdural lesions (Fig. 2). The created lesions were recognized and detailed. The specialist surgeon assessed the CT scan images, and subdural inflammation and brain lesions were confirmed. The results were similar across the control, treatment, and trauma groups.

Behavioral study

The present study evaluated the rats using the Morris Water Maze (MWM) test, a recognized method for assessing spatial learning and memory. This test measures their navigational skills and their instinct to escape from water, known as hydrophobia in rats. The

maze consists of a 30 cm deep pool with a hidden platform just below the surface. Initially, the rats swim freely and discover the platform through exploration. Over time, they learn to associate the platform's location with a visual cue on the pool wall, improving their navigational memory. Subsequent trials show a significant reduction in the time required to find the platform, indicating better memory retention and learning. This evidence highlights the effectiveness of the Morris Water Maze's (MWM) effectiveness for in studying cognitive function in rodents.

Ethical statement

The Ethics Committee of Baqiyatallah University of Medical Sciences confirmed this study.

Statistical analysis

SPSS-26 was used for data analysis; nonparametric tests were employed due to small sample sizes and non-normal distributions. Between-group comparisons were performed using Kruskal-Wallis tests with post hoc Dunn's tests, revealing significant differences in post-TBI outcomes. Within-group pre-post comparisons used Wilcoxon signed-rank tests, showing significant TBI-induced changes in treated groups. MWM data were analyzed using a two-way repeated measures ANOVA with Bonferroni correction, showing a significant group × time interaction. A P-value less than 0.05 was a statistically significant point.

Results

Morris blue conundrum test results

The MWM test results revealed distinct learning patterns across the three experimental groups (Sham, Control, and Nebivolol-treated) over the 21-day testing period. During the early acquisition phase (Days 8-14), both the Control (47.1 ± 1.5s) and Nebivolol (48.0 ± 1.0s) groups showed significantly longer escape latencies than Sham (36.2 ± 1.8s; $p < 0.05$), indicating an initial spatial learning impairment. However, in the late consolidation phase (Days 15-21), the Nebivolol group demonstrated remarkable improvement, achieving the shortest latencies (27.9 ± 1.4s) that were significantly shorter than those of both the Control (36.6 ± 1.5s, $p < 0.05$) and Sham (30.1 ± 2.1s) groups. This biphasic response—initial impairment followed by accelerated learning—resulted in Nebivolol-treated animals showing the most significant overall percentage improvement (41.9%) compared with the Control (22.3%) and Sham (16.8%) groups. Statistical analysis confirmed significant group ($F(2, 18) = 9.87$, $p = 0.001$), time ($F(13,234) = 15.43$, $p < 0.001$), and interaction effects ($F(26,234) = 2.11$, $p = 0.002$), suggesting that Nebivolol treatment differentially affected the temporal dynamics of spatial memory formation. These findings indicate that while Nebivolol may transiently impair early learning, it ultimately enhances late-phase memory consolidation in this model.

Table 1. Treatment effects on spatial learning in the MWM

Group	Early Phase Latency	Late Phase Latency	% Improvement	p-value (vs Sham)
Sham	36.2 ± 1.8	30.1 ± 2.1	16.8%	-
Control	47.1 ± 1.5*	36.6 ± 1.5*	22.3%	0.003
Nebivolol	48.0 ± 1.0*	27.9 ± 1.4†	41.9%†	<0.001

*= p<0.05 vs Sham
† = p<0.05 vs Control

Table 2. Vital signs measurements across treatment groups (Mean ± SD) with between-group comparisons

Parameter	Sham (n=7)	Nebivolol (n=7)	Control	p-value	(Median	Post-hoc Significance*
HR (bpm)	240.0 ± 8.9	239.7 ± 5.2	244.4 ± 5.3	0.826		NS
BR (breaths/min)	67.1 ± 2.9	56.1 ± 2.0	67.1 ± 6.7	0.008		Sham vs Neb: <0.05
BP (mmHg)	94.1 ± 3.8	78.7 ± 2.6	92.7 ± 3.5	0.005		Sham vs Neb: <0.01
T (°C)	37.57 ± 0.16	37.40 ± 0.33	37.36 ± 0.24	0.263		NS

Clinical results

The analysis of vital signs across treatment groups revealed significant physiological differences, particularly in respiratory and cardiovascular parameters (Table 2). While HR remained stable across all groups (Sham: 240.0 ± 8.9, Nebivolol: 239.7 ± 5.2, Control: 244.4 ± 5.3 bpm; $p = 0.826$), the Nebivolol group exhibited markedly lower respiratory rates (56.1 ± 2.0 breaths/min) compared to both Sham (67.1 ± 2.9) and Control (67.1 ± 6.7) groups ($p = 0.008$), with post hoc tests confirming these differences ($p < 0.05$). Blood pressure (BP) measurements showed a similar pattern, with Nebivolol-treated subjects demonstrating significantly lower values (78.7 ± 2.6 mmHg) than the Sham (94.1 ± 3.8) and Control (92.7 ± 3.5) groups ($p = 0.005$), with strong statistical significance in pairwise comparisons ($p < 0.01$). Core temperature (T) remained consistent across all groups (37.36-37.57°C; $p = 0.263$), indicating that thermoregulation was unaffected by the interventions.

Biochemical findings

The biochemical analysis revealed significant alterations following TBI across treatment groups. While all groups showed identical baseline erythrocyte sedimentation rates (ESR: 1.00 ± 0.00), post-TBI values diverged significantly (Sham: 1.00 ± 0.00, Nebivolol: 2.00 ± 0.00, Control: 3.00 ± 0.00; $p < 0.001$), with all pairwise comparisons being statistically significant ($p < 0.001$). Inflammatory markers showed distinct patterns: C-reactive protein (CRP) and cortisol levels increased substantially in both Nebivolol (CRP: 3.13 ± 0.12 to 5.49 ± 0.21; cortisol: 3.55 ± 0.20 to 5.60 ± 0.21) and Control groups (CRP: 3.06 ± 0.18 to 6.04 ± 0.13; cortisol: 3.42 ± 0.19 to 6.25 ± 0.09) post-TBI ($p = 0.018$ within groups, $p = 0.001$ between groups), while remaining stable in Sham animals. Prolactin levels decreased significantly in treated groups (Nebivolol: 0.085 ± 0.006 to 0.045 ± 0.002; Control: 0.083 ± 0.004 to 0.045 ± 0.003; $p \leq 0.018$) but not in Sham controls ($p = 0.075$). Notably, Nebivolol attenuated the increases in CRP and cortisol compared to Controls ($p = 0.001$), though both treatment groups differed significantly from Sham ($p < 0.001$). These findings demonstrate that TBI induces significant inflammatory and neuroendocrine responses that are differentially modulated by Nebivolol treatment, with particularly robust effects on acute-phase reactants and stress hormones (Table 3) (Fig. 1).

Table 3. Biochemical findings before and after TBI

Group	Parameter	Before	After	Within-Group	Between-Group	Pairwise Comparisons
Sham	ESR	1.00 ± 0.00	1.00 ± 0.00	-	**<0.001***	Sham vs. Nebivolol: **<0.001**, *Sham vs. Control:* **<0.001**
	CRP	3.29 ± 0.11	3.24 ± 0.10	0.172	0.174	-
	Cortisol	3.38 ± 0.12	3.39 ± 0.18	0.753	0.263	-
	Prolactin	0.088 ± 0.003	0.084 ± 0.004	0.075	0.558	-
Nebivolol	ESR	1.00 ± 0.00	2.00 ± 0.00	-	**<0.001***	Nebivolol vs. Control: **<0.001***
	CRP	3.13 ± 0.12	5.49 ± 0.21	**0.018***	**0.001***	Sham vs. Nebivolol: **<0.001**, *Nebivolol vs. Control:* **0.001**
	Cortisol	3.55 ± 0.20	5.60 ± 0.21	**0.018***	**0.001***	Sham vs. Nebivolol: **<0.001**, *Nebivolol vs. Control:* **0.001**
	Prolactin	0.085 ± 0.006	0.045 ± 0.002	**0.017***	**0.003***	Nebivolol vs. Control: 1.000 (NS), Nebivolol vs. Sham: **<0.001***
Control	ESR	1.00 ± 0.00	3.00 ± 0.00	-	**<0.001***	Control vs. Sham: **<0.001***
	CRP	3.06 ± 0.18	6.04 ± 0.13	**0.018***	**0.001***	Control vs. Sham: **<0.001***
	Cortisol	3.42 ± 0.19	6.25 ± 0.09	**0.018***	**0.001***	Control vs. Sham: **<0.001***
	Prolactin	0.083 ± 0.004	0.045 ± 0.003	**0.018***	**0.003***	Control vs. Sham: **<0.001***

Discussion

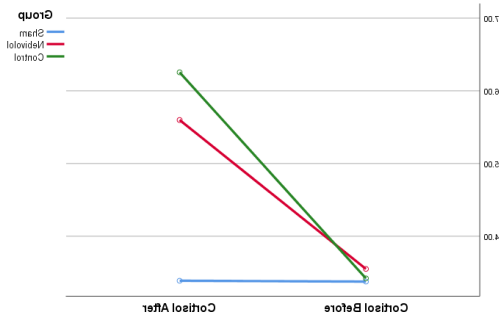
The study shows that TBI causes significant systemic changes, with Nebivolol revealing protective effects. This study demonstrates that Nebivolol treatment post-TBI significantly modulates inflammatory, neuroendocrine, and cognitive outcomes in a preclinical model, with significant implications for pediatric TBI, given developing brain's heightened exposure to oxidative stress and inflammation. Therefore, therapies that can safely interrupt these secondary injury cascades should be developed. The findings obtained position Nebivolol as a promising multi-mechanistic candidate for this role.

The study provides clear evidence that Nebivolol treatment significantly modulates multiple pathophysiological features in a rat model of mTBI. It indicates the neuroprotective, anti-inflammatory, and cardiovascular-stabilizing effects of Nebivolol treatment in a rat model of mTBI. The obtained results are consistent with prior research on Nebivolol effects.

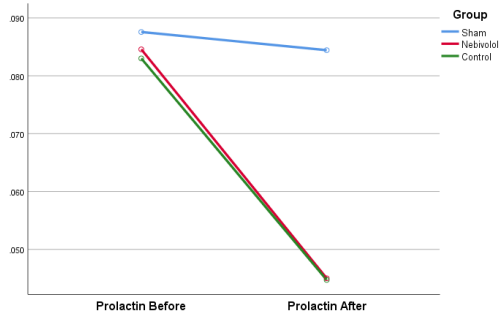
The MWM data demonstrated a biphasic cognitive response to Nebivolol: initial learning impairment during early acquisition (Days 8–14) followed by accelerated recovery in late consolidation (Days 15–21). The biphasic cognitive reaction in the MWM (initial impairment followed by accelerated rehabilitation) is especially intriguing in a developmental context. The improvement in escape latency in the Nebivolol group exceeds that of both the control and sham groups. It indicates enhanced neuroplasticity. In pediatrics, detaining injuries and facilitating the resumption of normal developmental trajectories are essential. The enhanced late consolidation aligns with evidence that Nebivolol improves cerebral blood flow via eNOS activation and may promote synaptic remodeling, both of which are vital for the recovering child's brain (14-18).

The delayed cognitive response (emerging > 2 weeks' post-injury) supports the idea that Nebivolol's neuroprotection affects secondary injury modulation rather than acute cytoprotection. This temporal profile reflects the clinical course of TBI recovery in which neuroinflammation rises days to week's post-injury (18-21).

A



B



C

Fig 1. Biochemical findings before and after TBI, A, CRP, B, cortisol and C, prolactin

Troost et al. demonstrated that Nebivolol reduces systemic oxidative stress (22-24). In addition, other studies documented that Nebivolol has estrogen receptor agonistic effects (25, 26). The neuroprotective effects of estrogen have been demonstrated in numerous studies (27, 28). A study showed that Nebivolol acts as an estrogen receptor agonist in neuronal cell lines and has neuroprotective outcomes (29). Another report discovered that Nebivolol has a neuroprotective impact via its antioxidant activity (30). Nebivolol is a potent third-generation beta-blocker with high selectivity for beta-1 adrenergic receptors, making it a practical therapeutic alternative for the control of cardiovascular diseases, especially hypertension. Considerable research, including studies by Troost et al., has revealed that Nebivolol effectively reduces systemic oxidative stress, a crucial factor in the evolution of various cardiovascular diseases (31).

Nebivolol significantly declined pro-inflammatory biomarkers (CRP, cortisol) compared to untreated TBI controls. While partially reversing TBI-induced prolactin suppression. These results confirm Nebivolol's established anti-inflammatory properties. The anti-inflammatory properties are vital for protecting the pediatric brain from inflammation-mediated damage to oligodendrocytes and neural precursors (3). The raised cortisol in untreated controls can be due to a maladaptive stress response linked to secondary neurodegeneration. The relief of the maladaptive cortisol stress response is particularly relevant. Prolonged exposure to glucocorticoids can damage hippocampal development and function. Nebivolol's ability to relieve this response without inducing hypotension. This offers a remarkable balance between glucocorticoid modulation and hemodynamic stability. Nebivolol performed this task without causing bradycardia or hypotension, a primary safety concern in pediatric TBI management.

The raised cortisol in untreated controls can be due to a maladaptive stress response linked to secondary neurodegeneration. Nebivolol's mitigation of this response—without inducing hypotension—suggests a unique balance between glucocorticoid modulation and hemodynamic stability. The reduction in prolactin in both TBI groups may be due to distribute of the hypothalamic-pituitary-adrenal (HPA) axis. This disruption was observed in human TBI but was minimally affected by Nebivolol, highlighting its selective anti-inflammatory action (18, 31).

Nebivolol preserved a stable heart rate (239.7 ± 5.2 bpm) while significantly reducing systolic blood pressure (78.7 ± 2.6 mmHg) and respiratory rate (56.1 ± 2.0 breaths/min) compared with controls. This contrasts with non-selective β-blockers (e.g., propranolol), which often cause bradycardia or hypotension in TBI. Nebivolol's cardioprotective profile likely arises from: 1. β1-selectivity with vasodilatory effects via NO release 9 (15, 31). Reduction in oxidative stress in vascular endothelium, improving perfusion, and 3. Inhibition of catecholamine surges without compromising cerebral autoregulation (18, 31).

This stability is critical in TBI, where hypotension aggravates ischemic injury. Notably, Nebivolol exceeded other vasodilatory β-blockers (e.g., carvedilol) in maintaining renal blood flow during rhabdomyolysis-induced injury, suggesting similar benefits in cerebral perfusion (31).

The persistent reduction in prolactin levels in Nebivolol-treated rats—despite attenuated cortisol/CRP responses—suggests unresolved HPA axis dysfunction. Prolactin is neuroprotective after brain injury, and its suppression may aggravate neuronal exposure. This suggests differential regulation of stress hormones: Cortisol (glucocorticoid) vs. prolactin (peptide hormone). Furthermore, it may reflect Nebivolol's limited blood-brain barrier permeability, which may limit direct pituitary modulation and TBI-induced dopaminergic dysregulation, as prolactin secretion is tonically inhibited by dopamine (31). In children, such neuroendocrine dysfunction can have profound consequences for growth, puberty, and metabolism, highlighting areas where Nebivolol's protection may be incomplete and where combined therapeutic approaches might be necessary.

This results in caution, as neuroendocrine dysfunction predicts poor long-term outcomes in TBI patients. Future studies should evaluate prolactin's role in Nebivolol-mediated neuroprotection.

The observation of early cognitive impairment with Nebivolol contrasts with studies showing immediate neuroprotection in stroke models 10. This difference may derive from several issues. One issue is the Timing of administration, specifically the delayed initiation (Day 8 post-TBI) compared to immediate post-injury dosing in other studies. Model-specific pathophysiology: Focal ischemia vs. diffuse axonal injury in pendulum-induced TBI is one such issue. Dose-dependent effects can cause this difference; lower doses (0.05 mg/kg) may initially fail to adequately target CNS receptors (14, 18, 31).

Clinically, beta-blockers reduce TBI mortality but increase risks of cardiopulmonary complications (18). Nebivolol's superior safety profile—due to NO-mediated vasodilation—may mitigate these risks, making it a promising candidate for translational studies (31).

Rasouli et al. (2023) reported the effect of buprenorphine in a rat model of moderate TBI. They showed that buprenorphine can increase subdural inflammation, reduce cortisol levels, and elevate prolactin levels. These biochemical changes suggest that buprenorphine causes neuroendocrine responses post-TBI, despite its limited impact on behavioral recovery. The findings are consistent with our study of Nebivolol's effects, particularly its ability to attenuate inflammatory markers such as CRP and cortisol. Both studies indicate a need for further investigation into dose-dependent effects and long-term functional outcomes (32).

The cardio protective and respiratory-stabilizing effects observed with Nebivolol are a significant advantage over non-selective beta-blockers. Its β1-selectivity and NO-mediated vasodilation likely prevent the harmful cardiopulmonary complications sometimes associated with other beta-blockers in critical care, making it a potentially safer option for children (18, 31).

Using young adult rats instead of juvenile animals is a limitation. Therefore, it is necessary to develop the brain's response to injury and therapy varies dramatically with age. Forthcoming investigations should explicitly use pediatric rodent models to assess age-specific effects directly. Additionally, analyzing the direct interaction between Nebivolol and the Nrf2 pathway in the developing brain will be necessary to elucidate its precise mechanism of action.

In conclusion, the present data provide clear preclinical evidence that Nebivolol modulates fundamental pathophysiological pathways in TBI. Nebivolol reduces inflammation, stabilizes cardiovascular function, and finally promotes cognitive rehab. The pleiotropic profile of Nebivolol promises reliable research in pediatric-focused models and forthcoming clinical trials.

In Conclusion

The present study demonstrated that Nebivolol treatment significantly improved TBI-induced physiological changes, including CRP and cortisol levels, while maintaining cardiovascular stability. Although it showed protective effects against TBI-related stress responses, the observed neuroendocrine alterations suggest complex systemic interactions.

Acknowledgment

This study was confirmed by the ethical committee of Baqiyatallah University of Medical Sciences with ethical cod: IR.BMSU.REC.1400.167.

Authors' contribution

Fathollah Ahmadpour, Samira Talebi, Mohammad Eslamian, Hamid Reza Rasouli; Data gathering: Mohammad Ali Akbar Esfahani, Hossein Faghih, Samira Talebi, Mohammad Eslamian, Hamid Reza Rasouli, Fathollah Ahmadpour; Data analysis: Mohammad Ali Akbar Esfahani, Hossein Faghih, Mohammad Eslamian, Hamid Reza Rasouli, Fathollah Ahmadpour; Data interpretation: Mohammad Ali Akbar Esfahani, Hossein Faghih, Samira Talebi, Mohammad Eslamian, Hamid Reza Rasouli, Fathollah Ahmadpour; manuscript drafting: Mohammad Ali

Akbar Esfahani, Hossein Faghih, Samira Talebi, Mohammad Eslamian, Hamid Reza Rasouli, Fathollah Ahmadpour

Conflict of Interest

The authors declared no conflict of interest.

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