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Original Article / Özgün Makale

The relationship of glycemic level with neurological outcomes during open cardiac surgery: A near-infrared spectroscopy study

Kalp ameliyatı sırasında nörolojik sonuçlar ile glisemik düzey arasındaki ilişki: Yakın kızılötesi spektroskopi çalışması

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ABSTRACT

Background: This study aims to investigate a possible relationship between blood glucose levels and neurocognitive functions in patients undergoing cardiopulmonary bypass.

Methods: Between December 2015 and February 2016, a total of 54 patients (42 males, 12 females; mean age 59.6±11.6 years; range, 31 to 83 years) undergoing elective cardiopulmonary bypass were prospectively included. Preparation for surgery, anesthesia, and standard data monitoring were performed in each patient with additional regional cerebral oxygen saturation monitorization. The patients underwent the Mini-Mental State Examination 24 h before and after the operation. Cerebral oximetry and blood glucose levels were sampled at pre-defined time points (T_0: before anesthesia; T_1: after anesthesia; T_2: after ischemia; T_3: after reperfusion, and T_4: after surgery).

Results: No statistically significant relationship was found in the different stages of cardiopulmonary bypass between the altered cerebral oxygen saturation values and blood glucose levels. There was no significant difference between the Mini-Mental State Examination scores of the patients with respect to either presence of diabetes mellitus or timing of the test.

Conclusion: Our study findings show that glycemic changes during cardiopulmonary bypass do not alter the regional cerebral oxygenation. In addition, when other variables are kept constant, changes in the blood glucose levels do not alter postoperative neurological functions.

Keywords: Cardiopulmonary bypass; glucose; Mini-Mental State Examination; regional cerebral oxygen saturation.

ÖZ

Amaç: Bu çalışmada kardiyopulmoner baypas yapılan hastalarda kan glukoz düzeyleri ve nörobilişsel fonksiyonlar arasındaki muhtemel ilişki araştırıldı.

Çalışma planı: Aralık 2015 - Şubat 2016 tarihleri arasında elektif kardiyopulmoner baypas uygulanan toplam 54 hasta (42 erkek, 12 kadın; ort. yaş 59.6±11.6 yıl; dağılım 31-83 yıl) prospektif olarak çalışmaya alındı. Her hasta için bölgesel serebral oksijen satürasyon monitörizasyonu ile birlikte cerrahi hazırlığı, anestezi ve standart veri takibi yapıldı. Hastalar ameliyattan 24 saat önce ve sonra Mini-Mental Durum Değerlendirmesi'ne tabi tutuldu. Serebral oksimetre ve kan glukoz düzeyleri önceden belirlenen zamanlarda örneklendi (T_0: anesteziden önce; T_1: anesteziden sonra; T_2: iskemi sonrası; T_3: reperfüzyon sonrası ve T_4: cerrahi sonrası).

Bulgular: Kardiyopulmoner baypasın farklı evrelerinde serebral oksijen satürasyon değerlerinde ve kan glukoz düzeylerinde görülen değişiklikler arasında istatistiksel olarak anlamlı bir ilişki bulunamadı. Diabetes mellitus varlığı veya testin zamanlaması açısından hastaların Mini-Mental Durum Değerlendirmesi skorları arasında da anlamlı bir fark yok idi.

Sonuç: Çalışma bulgularımız, kardiyopulmoner baypas sırasında glisemik değişikliklerin bölgesel serebral oksijenasyonda değişikliğe neden olmadığını göstermektedir. Ayrıca, diğer değişkenler sabit tutulduğunda, kan glukoz düzeylerindeki değişiklikler ameliyat sonrası nörolojik fonksiyonları değiştirmemektedir.

Anahtar sözcükler: Kardiyopulmoner baypas; glukoz; Mini-Mental Durum Değerlendirmesi; bölgesel serebral oksijen satürasyonu.

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Neurological outcomes are the most significant determinants of long-term quality of life following cardiac surgery in adults. Major risk factors associated with poor outcomes are embolism, hypoperfusion, and advanced age.[1] Intraoperative hyperglycemia is another risk factor which may worsen neurocognitive functions with decreased long-term survival and recurrent postoperative ischemic events, as the brain is highly susceptible to variations in blood glucose levels.[2] Hyperglycemia disrupts the normal coupling of cerebral metabolism with cerebral perfusion. Nevertheless, there is insufficient evidence for postoperative cognitive dysfunction related to poor glycemic control with cardiopulmonary bypass (CPB).

It is important to protect the brain precisely under surgical stress, as injuries caused by even subtle changes in blood pressure, glucose, and electrolyte values may result in functional losses.[3] Many intraoperative strategies are available to measure and reduce brain damage and improve surgical outcomes during CPB. However, none of the preventive measures has been proven to be fully effective, yet. Recently, non-invasive monitoring of regional cerebral oxygen saturation (rSO_2) by near-infrared spectroscopy (NIRS) has been introduced to evaluate the adequacy of tissue oxygenation.[4,5] In patients undergoing primary coronary artery bypass surgery, a significant association was found between prolonged cerebral desaturation demonstrated by the NIRS and early cognitive decline.[6] It is well-known that cerebral oxygen saturation can be affected by many factors such as, cerebral blood flow, cerebral metabolic rate, hemoglobin concentration, and arterial oxygen saturation.[4]

In the present study, the dynamic trends of cerebral oxygenation were investigated with blood glucose levels in patients undergoing CPB. We aimed to evaluate whether a potential relationship was present between regional cerebral oxygenation reflected by the NIRS and neurocognitive function tests and the blood glucose levels. Our secondary aim was to identify the difference between the patients with and without diabetes mellitus (DM) in terms of the NIRS and neurocognitive function tests during this period.

PATIENTS AND METHODS

The study protocol, which was designed according to the Ethical Principles for Medical Research involving Human Subjects outlined in the Declaration of Helsinki, was approved by our institutional Ethics Committee (No: 273, Date:23.12.2015; Yıldırım Beyazıt University Medical Faculty Ankara Atatürk Training and Research Hospital) and a written consent was obtained from each participant. A total of 54 patients (42 males, 12 females; mean age 59.6±11.6 years; range 31 to 83 years) who were classified according to the American Society of Anesthesiologists (ASA) Class II to IV and were scheduled for elective CPB were prospectively studied. Each patient was informed about the anesthetic procedure and study protocol in detail at the preoperative visit. Cognitive functions of the patients were assessed 24 h before and after the operation using the Mini-Mental State Examination (MMSE) test. Patients with preexisting neurological diseases (i.e., having a history of stroke or angiographic evidence or diagnosed with a 50% narrowing in a major cerebral or carotid artery or a previous surgery for such a disease), a preoperative MMSE score of <24, and severe vision and hearing problems influencing the quality of communication were excluded. Also, patients who underwent combined operations (i.e., simultaneous valve repair, carotid endarterectomy, or left ventricular aneurysm repair) were excluded. Before surgery, the patients underwent a thorough cardiac diagnostic work-up , including evaluation of the ejection fraction. Age, body mass index (BMI), medical history, current medications, preoperative left ventricular ejection fraction (%), and infarction time, if present, were recorded for each patient. All preoperative cardiac medications were continued until the morning of surgery, except for angiotensin-converting enzyme (ACE) inhibitors. Acetylsalicylic acid and thienopyridine therapy were discontinued one week before operation and replaced by subcutaneous doses of enoxaparin 1 $mg.kg^{-1}$ per day. Sulfonylurea derivatives were discontinued two days before surgery and replaced by insulin therapy.

Anesthetic and surgical procedure

All patients were premedicated with oral diazepam (5 mg) the night before and intramuscular morphine sulfate (0.1 $mg.kg^{-1}$) 45 min before surgery. Non-invasive monitoring was established and radial artery was cannulated under local anesthesia. This procedure enabled invasive monitoring of arterial blood pressure. It was also used to obtain blood samples required for the blood gas analysis. The NIRS probes were applied bilaterally to the forehead of the patients before the induction of anesthesia and cerebral oxygen saturation was continuously measured using the INVOS 5100 regional oximeter (Somanetics Corporation, Troy, Michigan, USA) and recorded for the duration of the operative procedure and in the intensive care unit (ICU) until 24 h postoperatively.[7] The anesthesiologists

reversed any 10% decline in the rSO_2 values for a duration exceeding 15 sec relative to the baseline value according to an interventional algorithm.[8] Anesthesia was similar for all patients, and consisted of 10 $\mu g.kg^{-1}$ fentanyl in combination with 3-5 $mg.kg^{-1}$ thiopental sodium and 0.6 $mg.kg^{-1}$ rocuronium bromide given intravenously at induction. After intubation, anesthesia was maintained by additional doses of fentanyl (5 $\mu g.kg^{-1}$) and rocuronium bromide (0.03 $mg.kg^{-1}$), and by inhalation of 0.5 to 2% sevoflurane. The depth of anesthesia during surgery was between 40-60 according to the bispectal index (BIS XP™; Aspect Medical Systems, Newton, MA, USA). The patients received air and oxygen (fractional inspired oxygen concentration of 50%) throughout surgery. Ventilation during the anesthesia was performed in a volume-controlled mode. Respiratory rate and tidal volume were adjusted in the way that normocapnia was achieved. Preparation for surgery, anesthesia, and perioperative vital data monitoring (five-channel electrocardiography, pulse oximetry, capnography, nasopharyngeal and rectal temperature, arterial blood pressure, and central venous pressure [7F Arrow, Erdingen, Germany]) were done in the same standardized way for each patient. During surgery, a median sternotomy was made, heparin was given (350 IU kg^{-1}), aortic and right atrial venous cannulas were inserted, and a standard CPB with moderate systemic hypothermia (28 °C to 30 °C of nasopharyngeal temperature) was instituted using a Jostra HL 20 hollow-fiber membrane oxygenator and a roller-pump generating a non-pulsatile flow. Activated coagulation time (ACT) was kept above 450 sec throughout the CPB period. An arterial filter was included in the circuit. A standard pump priming solution was used in each patient. Routine surgical technique and cardioprotective strategies were used in all patients. For myocardial protection, the aorta was cross-clamped and cold anterograde and retrograde intermittent cardioplegia (Plegisol® Abbott, North Chicago, IL, USA) were used. In addition, CPB flow was maintained between 2.2 L $min^{-1}.m^{-2}$ and 2.5 L $min^{-1}.m^{-2}$. The mean perfusion pressure was maintained between 50 and 80 mmHg on bypass. Vasopressors and vasodilators were administered, where necessary. Hematocrit concentrations were maintained above 21% during bypass. We targeted to achieve a blood glucose level of 140 to 200 $mg.dL^{-1}$ in all patients.[9] The blood glucose levels >200 $mg.dL^{-1}$ were intervened by continuous insulin infusion (50 IU regular insulin in 500 mL of dextrose 10% in water in a range of 1 IU to 5 IU h^{-1}). Blood glucose levels which fell below that range resulted in termination of the insulin infusion.

After the surgical procedure, reperfusion of the heart and rewarming to temperature of 36 °C, the heart was placed in atrioventricular mode at a rate of 90 bpm, and the patients were separated from CPB. After removal of the aortic cannula, heparin activity was neutralized with protamine at a ratio of 1 mg of protamine per 100 U heparin. Protamine administration was further guided by ACT measurements aiming at 140 sec. When the mean arterial pressure was below 60 mmHg, vasopressor

Table 1. Demographic, clinical and operative data of patients (n=54)

Variables	All patients		
	n	%	Mean±SD
Age (year)			59.6±11.6
Gender			
Male	42	77.8	
Female	12	22.2	
Body mass index			24.3±2.5
Preoperative complications*			
Diabetes mellitus	18	33.3	
Hypertension	7	12.9	
Chronic obstructive lung disease	5	9.2	
Smoking history	33	61.1	
Chronic renal failure	18	33.3	
Surgical history	20	37.0	
EuroSCORE II			5.1±4.7
Operation time (min)			234±63
Cardiopulmonary bypass time (min)			132.7±53.5
Aortic cross-clamp time (min)			100.6±44.5

SD: Standard deviation; * Some patients overlap in this category.

therapy was initiated. During surgery, we recorded the duration of aortic clamping and CPB, volume of cardioplegic solution used, volume of hemodilution and infusions, diuresis, and minimum body temperature. At the end of the surgical procedure, the patients were transferred to the ICU. When hemodynamically stable and rewarmed, the patients were weaned from the ventilator and extubated.

At five time points, the blood samples were collected and the reference level (T_0) was able to be obtained immediately after the cannulation of the arterial system and before anesthesia; the second sample (T_1) was taken 20 min after anesthesia was introduced; the third sample (T_2) was taken after 20 min of the aortic cross-clamp; the fourth sample (T_3) was taken 20 min after the removal of the aortic cross-clamp; and the final sample (T_4) was obtained by venipuncture 24 h after the surgery. The serum electrolytes (K^+, Na^+, Ca^{2+}) and hemoglobin, hematocrit, blood glucose, lactate, and arterial blood gases were measured using the blood samples taken from the radial artery.

Table 2. Blood gas analysis values according to measurement times with respect to presence of diabetes mellitus

		T_0	T_1	T_2	T_3	T_4
	n	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
pH						
DM (-)	36	7.5±0.0	7.4±0.0	7.4±0.1**	7.4±0.1**	7.4±0.1**
DM (+)	18	7.5±0.0	7.4±0.0*	7.4±0.1**	7.4±0.1**	7.4±0.0**
p		0.293	0.074	0.502	0.412	0.051
PaO_2						
DM (-)	36	117.5±46.5	194.4±74.5**	264.6±74.5**	225.5±56.9**	193.1±65.7**
DM (+)	18	151.8±100.7	193.3±37.0	262.9±66.4**	209.9±58.5*	173.6±59.9
p		0.777	0.831	0.809	0.393	0.310
$PaCO_2$						
DM (-)	36	35.4±2.8	33.7±5.0	35.8±5.4	38.1±6.6*	36.4±5.0
DM (+)	18	33.3±4.6	37.9±16.6	38.9±16.3	35.8±3.9	35.9±3.6*
p		0.076	0.541	0.872	0143	0.678
BE						
DM (-)	36	1.9±3.3	-0.5±2.1**	-2.9±2.1**	-3.0±2.2**	-3.5±1.8**
DM (+)	18	0.5±2.0	-1.5±2.3**	-3.1±2.3**	-3.6±2.4**	-2.7±2.0**
p		0.216	0.159	0.800	0.474	0.166
HCO_3						
DM (-)	36	25.1±2.0	23.0±1.9**	21.6±1.8**	21.5±2.1**	21.0±1.8**
DM (+)	18	23.5±2.1	22.1±2.2**	21.3±2.0**	20.6±2.4**	21.4±1.9**
p		0.025	0.432	0.809	0.315	0.489
Lactate						
DM (-)	36	1.0±0.2	1.1±0.7	3.7±1.0**	2.7±0.9**	3.4±1.3**
DM (+)	18	1.0±0.3	1.0±0.4	3.7±1.3**	3.1±1.2**	2.7±1.1**
p		0.551	0.364	0.853	0.309	0.104
Glucose						
DM (-)	36	114.8±15.8	117.8±18.2	153.4±47.6**	210.3±39.9**	230.7±45.8**
DM (+)	18	164.4±43.5	163.8±38.8	173.1±49.6	217.4±51.3**	232.6±55.8**
p		<0.001	<0.001	0.137	0.800	0.588
rSO_2 right						
DM (-)	36	62.9±10.6	60.3±9.3*	47.8±10.4**	48.5±10.6**	56.5±12.0**
DM (+)	18	57.6±10.5	56.3±11.1	50.9±5.0*	50.1±7.7*	58.0±6.9
p		0.116	0.149	0.124	0.917	0.764
rSO_2 left						
DM (-)	36	61.2±10.6	58.8±9.5	46.0±10.0**	46.1±11.3**	55.6±12.3**
DM (+)	18	62.9±10.6	58.8±10.4	49.1±5.4**	49.7±8.5**	58.5±7.9
p		0.510	0.755	0.480	0.460	0.518

SD: Standard deviation; DM: Diabetes mellitus; PaO_2: Arterial partial pressure of O_2; $PaCO_2$: Arterial partial pressure of CO_2; BE: Base excess; HCO_3: Bicarbonate; rSO_2: Regional cerebral oxygen saturation; * p<0.05; **p<0.01 (compared to T_0)

Sample size estimation

The primary end point of this study was defined as a positive correlation between the changes in blood glucose levels and regional cerebral saturation values at five critical time points of CPB. Sample size estimation was performed using the Power and Sample Size (PASS) version 11 for Windows software. (SPSS Inc., Chicago, IL, USA) According to the recent references reported in the literature, the sample size was predetermined by with a power analysis of 80.34% which showed at least 43 patients to be sufficient.

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented in mean ± standard deviation (SD), and frequency (percentage). Normal distribution of the variables was tested by visual (histogram and probability graphs) and analytical methods using the Shapiro-Wilk test. For the evaluation of the statistical significance between two independent groups, the Mann-Whitney U test was used, while to assess the statistical significance between two dependent groups, the Wilcoxon signed-rank test was used. In case of more than two dependent groups, the Friedman test was used for abnormally distributed variables. In case of a statistically significant difference between more than two dependent groups, post-hoc Bonferroni correction was used. The correlation between variables was assessed using the Spearman's correlation test. A p value of <0.05 was considered statistically significant.

RESULTS

Of a total of 54 patients, 18 were with controlled DM and 36 were without DM. Demographic and clinical characteristics of the patients are summarized in Table 1. The mean duration of DM was 10.0±8.6 (range, 1 to 22) years. Among these patients, three of them were treated with insulin, while the others were controlled by oral hypoglycemic agents. As for the cerebral oxygen saturation, both right and left hemispheric rSO_2 values decreased at all time points, compared to the baseline values following the induction of anesthesia, and also compared to each previous measurement, except for the postoperative values. The decrease was significant at T_2 compared to T_0, T_1, and T_4 ($p<0.001$) (Table 2). As expected in ischemia and reperfusion periods of bypass, blood glucose levels increased and rSO_2 values decreased.

The correlation analysis revealed that neither right nor left hemisphere rSO_2 values had a linear correlation with blood glucose levels (p=0.468, p=0.632; respectively). However, changes in the rSO_2

Table 3. The correlation between blood glucose levels, right and left hemispheric rSO_2 values (n=54)

	Mean glucose	Mean rSO_2 right	Mean rSO_2 left
Mean glucose			
r*	1	0.101	0.067
p	-	0.468	0.632
Mean rSO_2 right			
r*	0.101	1	0.767
p	0.468	-	<0.001
Mean rSO_2 left			
r*	0.067	0.767	1
p	0.632	<0.001	-

* Pearson correlation coefficient.

Table 4. Mini-Mental State Examination values at pre- and postoperative period

	Preoperative	Postoperative	
	Mean±SD	Mean±SD	*p*
Mini-Mental State Examination			
Diabetes mellitus (-)	29.9±3.4	29.8±5.2	>0.05
Diabetes mellitus (+)	28.8±5.3	27.1±6.0	>0.05
p	>0.05	>0.05	

SD: Standard deviation.

values of each hemisphere were similar to each other (Table 3). There was no significant difference between pre- and postoperative MMSE scores of patients with and without DM ($p>0.05$) (Table 4).

DISCUSSION

Vascular complications associated with diabetes have profound effects on cerebral circulation. It has been reported that chronic hyperglycemia decreases elasticity of smooth muscle cells, reducing the ability of blood vessels to maintain sufficient blood and nutrient supply to brain tissue.[10,11] In addition, vascular impairment has been found to increase the risk of neurological events, as seen by the increased risk of transient ischemic attack and stroke by two to five-fold in diabetic individuals.[12,13] The effects of acute hyperglycemia on endothelial functions are deleterious by apoptosis or exaggeration of ischemia reperfusion cellular injury.[14-16] To date, no study on the instant effects of changing blood glucose levels on cerebral metabolism and cognitive functions detected by the NIRS in cardiac surgery has been reported in the literature. Similarly, our study was unable to demonstrate any significant relationship between the instant blood glucose levels and regional cerebral oxygen saturation at different time points of cardiac surgery in patients either with controlled DM or without DM.

Many pathological changes caused by hyperglycemia have been demonstrated in the small vessels, arteries, and peripheral nerves. Vascular endothelial cells are damaged by hyperglycemia, although the causative mechanisms have not been elucidated, yet.[17] Several authors have reported that hyperglycemia may lead to endothelial dysfunction and exacerbate tissue damage with cerebrovascular changes both during ischemia and reperfusion.[18,19]

In recent studies, a decline in the jugular bulb oxygen saturation during normothermic CPB was reported to be associated with postoperative short-term cognitive deficits in diabetic patients.[20,21] However, rSO_2 and jugular bulb oxygen saturation is useful to measure different entities; therefore, expecting that they can be used interchangeably can be misleading. In diabetics, the pathway of nitric oxide is mostly affected and the cerebral endothelial function is altered extensively in CPB.[22] As a result, diabetic patients lose the normal coupling of cerebral blood flow with metabolism during CPB and usual cerebral blood flow-perfusion pressure relationship. Thus, a direct effect of blood glucose level on cerebrovascular reserve may be out of the question. However, in case of vascular reactivity as in CPB, this effect can be a contributory factor.

Many studies have suggested that the normal coupling of cerebral blood flow with metabolism and usual cerebral blood flow-perfusion pressure relationship is lost in diabetic patients during CPB, resulting in cerebral desaturation, which is also reported to be closely related to postoperative neurological disorder.[23,24] This may be associated with the brain's being more susceptible to hypoxia than other organs. Nevertheless, the diabetic patients did not make any difference in the rSO_2 values and postoperative neurological test scores from the non-diabetic ones in our study, probably due to our tight control of all factors playing a role in this aspect.

During cardiac surgery, the pre-bypass and early post-bypass periods are vulnerable times for the provision of adequate cerebral oxygenation due to blood-pressure instability. Our study demonstrated a gradual decline in rSO_2 following the onset of CPB and at the time of aortic cross-clamping due to decreased mean arterial pressure and cerebral perfusion pressure. These time points also corresponded to increased blood glucose levels. However, we made interventions to avoid any increase in the blood glucose levels in this study. Besides, we kept the bispectral index between 40 and 60, assuming to keep the cerebral metabolic rate constant during surgery.

The preservation of cerebral oxygen saturation is a major concern in cardiac surgery.[6] Ellis et al.[25] demonstrated that various factors, such as hemoglobin concentrations, extra-cranial blood flow, and altered cerebral arterial to venous blood volume ratio, had an effect on the NIRS measurements. Hemodilution at the start of CPB also causes a decline in rSO_2. Other critical times for desaturation are the low perfusion pressure and early rewarming stages. In addition, the temperature of CPB remains a subject of debate. Hypothermia reduces tissue metabolic demands, but may impair the autoregulation of cerebral blood flow and contribute to neurological morbidity. Some authors reported a worse neurological outcome of normothermic bypass (37 °C) compared to that of moderately hypothermic (32 °C) perfusion.[26,27] In the present study, a moderately hypothermic bypass was used.

In this study, we assessed the cognitive functions using the MMSE test which has been shown to be a valid and reliable method for its brevity and suitability for bedside use. The absence of a significant difference between pre- and postoperative MMSE values either in diabetics or non-diabetics; could be explained

by prompt intraoperative interventions to preserve homeostasis. On the other side, after the surgery, the patients were followed intubated in ICU for four to six h; thus, we performed postoperative MMSE test at 24 h after surgery. Chen et al.[28] demonstrated the importance of timing of MMSE in the postoperative period after hip or knee arthroplasty. The authors found significant cognitive dysfunction in 51% of the patients at one hour after surgery, which disappeared in 85% of the patients at three hour after surgery. At 24 h after surgery, only one of 70 patients showed cognitive dysfunction. These results are consistent with our findings showing normal cognitive function at 24 h after surgery. However, more precise results and evaluations could have been made, if the patients were tested at earlier hours after anesthesia.

Nonetheless, there are some limitations to this study. A larger sample size with repeated cognitive function tests both in the early and long-term postoperative periods might confirm our results. Based on our results, we found no relationship between blood glucose levels and regional cerebral oxygen saturation as assessed by the near-infrared spectroscopy. Thus, as a secondary endpoint of this study, none of the patients undergoing cardiopulmonary bypass had unfavorable neurological outcomes.

In conclusion, changing trends of regional cerebral oxygenation don't reflect glycemic changes during CPB. In the present study, variables were kept strictly constant. Therefore, there is a need for further research in this aspect.

Declaration of conflicting interests

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