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Original Article

Antithrombotic effect of epigallocatechin gallate on the patency of arterial microvascular anastomoses

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Background Microvascular anastomosis patency is adversely affected by local and systemic factors. Impaired intimal recovery and endothelial mechanisms promoting thrombus formation at the anastomotic site are common etiological factors of reduced anastomosis patency. Epigallocatechin gallate (EGCG) is a catechin derivative belonging to the flavonoid subgroup and is present in green tea (*Camellia sinensis*). This study investigated the effects of EGCG on the structure of vessel tips used in microvascular anastomoses and evaluated its effects on thrombus formation at an anastomotic site.

Methods Thirty-six adult male Wistar albino rats were used in the study. The right femoral artery was cut and reanastomosed. The rats were divided into two groups (18 per group) and were systemically administered either EGCG or saline. Each group were then subdivided into three groups, each with six rats. Axial histological sections were taken from segments 1 cm proximal and 1 cm distal to the microvascular anastomosis site on days 5, 10, and 14.

Results Thrombus formation was significantly different between the EGCG and control groups on day 5 (P = 0.015) but not on days 10 or 14. The mean luminal diameter was significantly greater in the EGCG group on days 5 (P = 0.002), 10 (P = 0.026), and 14 (P = 0.002). Intimal thickening was significantly higher on days 5 (P = 0.041) and 10 (P = 0.02).

Conclusions EGCG showed vasodilatory effects and led to reduced early thrombus formation after microvascular repair. Similar studies on venous anastomoses and random or axial pedunculated skin flaps would also contribute valuable findings relevant to this topic.

Keywords Microsurgery / Thrombosis / Catechin / Oxidants / Vasodilatation

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INTRODUCTION

The patency of microvascular anastomoses is adversely affected by local and systemic factors [1]. Impaired intimal recovery and endothelial mechanisms promoting thrombus formation at the anastomotic site are common causes of decreased anastomosis

patency [1-4]. Dextran, heparin, low-molecular-weight heparin, and steroids are commonly administered in clinical practice to prevent thrombus formation. Several drugs, including vinblastine, sildenafil, and botulinum toxin, have been used to increase anastomosis patency in experimental studies; however, the clinical applications of these drugs are currently limited [1,2,5,6].

Epigallocatechin gallate, found in green tea (*Camellia sinensis*), is a catechin derivative belonging to the flavonoid subgroup that has been shown to exert cardioprotective, anti-atherosclerotic, anti-oxidant, vasorelaxant, anti-aggregant, and anti-inflammatory effects [7-11]. It was also shown to prevent vascular smooth muscle hypertrophy and intimal hyperplasia, to accelerate pseudointima and intima formation, to stimulate endothelial nitric oxide production, to inhibit plasminogen activator inhibitor-1 production, and to prevent thrombocyte aggregation [12]. The purpose of the present study was to investigate the effects of epigallocatechin gallate on the structure of vessel tips used in microvascular anastomoses and to determine its effects on thrombus formation at the anastomotic site.

METHODS

This study was approved by the Ankara University Medical Faculty Laboratory Animals Ethics Committee (approval number: 53184147-50.04.04/3835). Thirty-six adult male Wistar albino rats weighing 300–400 g were included in the present study. The rats were kept individually under a 12-hour dark/12-hour light cycle. The room temperature and humidity were maintained at 22°C and 30%, respectively. Animals were provided with food and water ad libitum. The rats were divided into two groups, each consisting of 18 animals. The groups were systemically administered either epigallocatechin gallate or saline, as described in more detail below. Each group was further divided into three subgroups, each containing six rats. Axial sections measuring 1-μm thick were cut and collected from segments 1 cm proximal and 1 cm distal to the microvascular anastomoses at 5, 10, and 14 days after anastomosis. These time-points were chosen because day 5 corresponds to the time of pseudointima formation and day 14 to permanent intima formation. Day 10 was chosen in order to evaluate whether permanent intima formation was accelerated. One rat died due to the anesthesia and two rats developed wound infections during follow-up. The infected rats were excluded, and two healthy rats were included instead. Postoperative analgesia was achieved via 700 mg/kg acetaminophen. After collecting tissue samples at the indicated time points, the rats were sacrificed by cervical dislocation under general anesthesia.

Surgical technique for anastomosis

General anesthesia was achieved by intraperitoneal administration of 50 mg/kg ketamine HCl (Ketalar; Eczacıbaşı, İstanbul, Turkey) and 10 mg/kg xylazine hydrochloride (23.32 mg/mL; Rompun, Bayer Korea, Seoul, Korea). Intramuscular chlortetracycline (Devamisin; Damla İlaç, İstanbul, Turkey) was administered at a dose of 10 mg/kg as prophylaxis against infection. The right inguinal region of each rat was shaved and sterilized with Betadine solution. The region of interest was accessed by an incision in the inguinal crease. The femoral artery was dissected and prepared. A complete transverse incision was then made using straight microsurgical scissors. Vessel tips were prepared and end-to-end microvascular anastomoses were performed with eight stitches using 10/0 nylon monofilament sutures (Ethilon; Ethicon, Johnson & Johnson, Somerville, NJ, USA). All anastomoses were carried out by the same experienced researcher who was blinded to the experimental groups.

Drug administration

Rats in the experimental group were administered epigallocatechin gallate (Sigma-Aldrich Co., St. Louis, MO, USA) once before surgery and once daily after surgery at a dose of 1 mL of epigallocatechin gallate solution prepared as 100 mg/kg via gastric gavage. The rats in the control group were given equivalent volumes of saline via gavage. The doses and administration protocol were previously described by Meng et al. [13], Choi et al. [14], Unno and Takeo [15].

Assessment of arterial patency

On days 5, 10, and 14 after surgery, the rats were re-operated under general anesthesia as described above. The femoral artery and vein were exposed through initial incisions, and dissected free of the adjacent tissues. Vessel patency was assessed by the "milking" test. There were no physical or macroscopic signs of thrombotic complications.

Histopathology

Simultaneously with the arterial patency assessment, rats were also examined for signs of infection or abscess formation at the anastomotic site. Rats with any of these signs were excluded from the study. In rats with a visible anastomotic site, tissue samples were collected from segments 1 cm proximal and 1 cm distal to the anastomotic site. Light microscopy was performed after irrigating the samples with saline to measure luminal diameter and intimal or medial thickening. All tissues were stored in 10% neutral-buffered formalin solution, embedded in paraffin, and stained with hematoxylin and eosin. Axial 1-μm tissue sections were obtained from segments 1 cm proximal and 1 cm

Table 1. Histopathological criteria

Factor	Criterion	Grade
Thrombus formation (fibrin deposition on the vessel wall)	< 1/3 Of the luminal diameter	+
	1/3–2/3 Of the luminal diameter	++
	> 2/3 Of the luminal diameter	+++
Deficiency of elastic lamina	< 1/3 Of the luminal circumference	+
	1/3–2/3 Of the luminal circumference	++
	> 2/3 Of the luminal circumference	+++
Intimal thickening	1–2 Cells thick	+
	2–5 Cells thick	++
	> 5 Cells thick	+++
Medial thickening	Mild	+
	Moderate	++
	Marked	+++
Adventitial inflammation	Few lymphocytes	+
	Moderate	++
	Marked	+++
Foreign body reaction around the suture	Few lymphocytes	+
	Lymphocytes and few giant cells	++
	Diffuse lymphocytes and multiple giant cells	+++

distal to the anastomotic site. They were then examined by the same pathologist/histologist under a light microscope, applying macroscopic and microscopic histopathological criteria (Table 1). Macroscopic features included an increase in vessel diameter or a change in color. Microscopic features included thrombus formation, deficiency of the elastic lamina, intimal thickening, medial thickening, adventitial inflammation, foreign body reactions, and the mean luminal diameter (in millimeters) (Table 1).

Statistical analysis

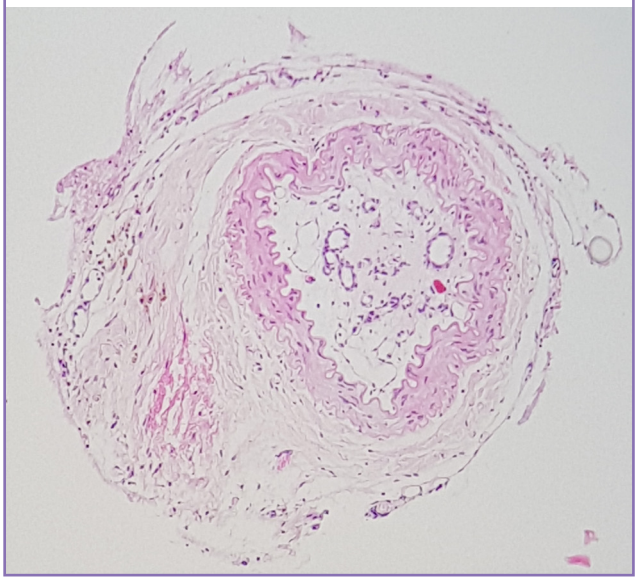
Of the histopathological variables, the mean luminal diameter was expressed numerically, while the others were expressed ordinally (Table 1). In the descriptive statistics related to the data, median, minimum, and maximum values were calculated. The Mann-Whitney U test was used to compare measurements between groups. P-values < 0.05 were considered to indicate statistical significance. All analyses were performed using SPSS version 21 (IBM Corp., Armonk, NY, USA).

RESULTS

The histopathological results of all rats are presented in Table 2. The increase in mean vascular luminal diameter was significantly higher in the epigallocatechin gallate group on day 5 ($P = 0.002$), day 10 ($P = 0.026$), and day 14 ($P = 0.002$). The macroscopic color change was significantly different between groups, and the vessels were redder on only day 10 ($P = 0.015$), not on days 5 or 14. Thrombus formation was significantly less frequent in the epigallocatechin gallate group on day 5 ($P = 0.015$), but not on days 10 or 14 (Fig. 1). No significant differences were found in terms of deficiency of the elastic lamina, adventitial inflammation, and vascular foreign body reactions on days 5, 10, or 14 between the groups. Additionally, severe arterial luminal narrowing resulting from intimal thickening was seen in the control group on day 10 (Fig. 2). Medial thickening was not significantly different between groups. The most striking difference was found in the mean luminal diameter, which was significantly greater in the epigallocatechin gallate group on days 5 ($P = 0.002$), 10 ($P = 0.026$), and 14 ($P = 0.002$) (Table 3).

Fig. 1. Organized thrombus

Total arterial occlusion in the control group on day 5. Some recanalization areas can be seen at the center of the thrombus. Mild medial thickening was seen (H&E, × 10). Thrombus formation was frequent in the control group. There were no thrombus formation in the epigallocatechin gallate group on day 5.



DISCUSSION

Arterial problems, especially occlusions, still pose challenges in microsurgery. Various drugs and experimental models are used to manage arterial problems in microsurgery practice.

Rats were used in this experimental study since they are commonly used to practice surgical techniques and to establish experimental models of microsurgery, such as thrombus formation after microanastomosis. The similar pharmacokinetic properties of epigallocatechin gallate in rats and humans was another reason for preferring rats in this study. All technical and environmental factors were standardized throughout the study. Because the diameter of the rat femoral artery is equivalent to the diameter of the human digital artery, which is involved in

Table 2. Histopathological findings

No	Group	Diameter increase	Color change	Presence of a thrombus	Deficiency of the elastic lamina	Intimal thickening	Medial thickening	Adventitial inflammation	Foreign body reaction	Mean luminal diameter (mm)
1	C5	–	–	–	–	–	–	+	+	0.3
2	C5	–	–	+++	–	–	–	+	+	0
3	C5	–	–	+++	+	+	–	–	+	0
4	C5	–	+	+++	+	–	–	+	++	0
5	C5	–	–	+++	–	–	–	–	+	0
6	C5	–	–	+++	+	–	–	–	–	0
7	C10	+	+++	–	++	+	–	+	++	0.2
8	C10	–	–	–	+	–	–	+	++	0.3
9	C10	++	++	–	++	–	+	+	+	0.3
10	C10	+	+	–	+	+	–	+	++	0.4
11	C10	–	+	++	–	–	–	–	+	0.2
12	C10	–	+	++	–	–	–	–	+	0.1
13	C14	+	–	+++	+	–	–	+	++	0
14	C14	–	–	–	+	+++	–	+	++	0.1
15	C14	–	–	+++	+	–	–	+	+	0
16	C14	–	–	–	++	++	–	+	+++	0.3
17	C14	+++	+	–	–	–	–	+	+	0.3
18	C14	+	+	++	–	–	–	–	+	0.2
19	D5	+	–	–	+	++	++	+	+	0.5
20	D5	+	–	–	++	++	–	+	+	0.5
21	D5	–	–	–	+	+	–	–	+	0.5
22	D5	–	–	–	–	–	–	+	+	0.4
23	D5	+	+	–	+	+	+	–	–	0.4
24	D5	+	+	–	+	+	+	–	–	0.4
25	D10	–	–	–	++	++	–	+++	++	0.5
26	D10	–	–	–	–	+	–	++	++	0.4
27	D10	–	–	–	–	+	+	+	+	0.4
28	D10	–	–	–	–	++	–	+	+	0.4
29	D10	+	–	–	–	+	+	–	–	0.4
30	D10	+	–	–	–	+	+	–	–	0.3
31	D14	–	–	+	+	–	–	+	++	0.5
32	D14	–	–	–	+	+	–	+	+	0.4
33	D14	–	–	–	+	+++	–	+	+	0.4
34	D14	–	–	–	+	++	+	+++	–	0.5
35	D14	–	–	–	+	–	–	++	++	0.4
36	D14	+	–	–	+	–	–	–	–	0.5

C, control group; D, drug (epigallocatechin gallate) group; 5, day 5; 10, day 10; 14, day 14.

finger replantation, it was considered to be appropriate to use the rat femoral artery. In order to obtain homogeneous luminal vessel diameter data, only male rats with similar weights were included.

In addition to surgical and technical factors, the success of microsurgery is closely related to patients' health status, health problems, and medications. Several studies have examined the effects of various substances, including low-molecular-weight heparin, steroids, sildenafil, and vinblastine, on enhancing microvascular anastomosis patency [1-6]. However, the benefits of these substances have not been proven. Epigallocatechin gallate was used in our study, as it possesses cardioprotective, anti-atherosclerotic, anti-oxidant, vasorelaxant, anti-aggregant, and anti-inflammatory properties [7-12].

In previous studies, epigallocatechin gallate has been shown to ameliorate brain damage after cerebral artery occlusion [14] and to improve the viability of rat perforator abdominal flaps [16]. Furthermore, epigallocatechin gallate has been suggested to reduce ischemia-reperfusion injuries in rat epigastric island flap [17] and to improve the survival of random-pattern skin flaps [18].

Histopathological assessments of the microanastomosis site were made on days 5, 10, and 14. Day 5 was chosen as a time point because most replanted limbs or free flaps are lost within the first 5 days. Such losses have been attributed to inflammatory cell migration damaging the endothelium and promoting

Fig. 2. Intimal thickening

(A) No intimal thickening in a histologically normal vessel in the epigallocatechin gallate group on day 10 (H&E, ×10). (B) Severe arterial luminal narrowing caused by intimal thickening in the control group on day 10 (yellow arrow). More than five cells are seen in the intima (H&E, ×10). Intimal hyperplasia is a cause of arterial occlusion and failure of anastomosis. Epigallocatechin gallate prevents intimal hyperplasia and accelerates pseudointima and intima formation, stimulating endothelial nitric oxide production.

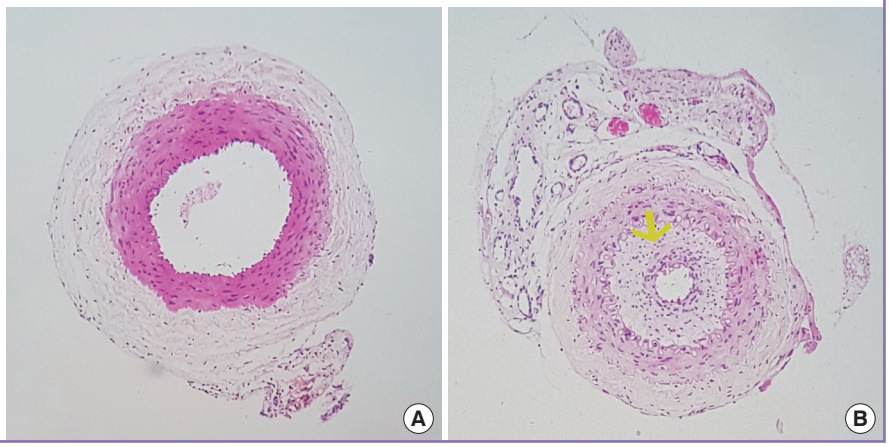


Table 3. Descriptive statistics and comparison of histopathological results between groups

Histopathological results		Control group, median (min to max)	Drug group, median (min to max)	P-value[a]
Diameter increase	Day 5	– (– to –)	+ (– to +)	0.065
	Day 10	+ (– to ++)	– (– to +)	0.589
	Day 14	+ (– to +++)	– (– to +)	0.310
Color change	Day 5	– (– to +)	– (– to +)	0.699
	Day 10	+ (– to +++)	– (– to –)	0.015[b]
	Day 14	– (– to +)	– (– to –)	0.394
Presence of trombus	Day 5	+++ (– to +++)	– (– to –)	0.015[b]
	Day 10	– (– to ++)	– (– to –)	0.394
	Day 14	+ (– to +++)	– (– to +)	0.240
Deficiency of elastic lamina	Day 5	+ (– to +)	+ (– to ++)	0.240
	Day 10	+ (– to ++)	– (– to ++)	0.240
	Day 14	+ (– to ++)	+ (+ to +)	0.699
Intimal thickening	Day 5	– (– to +)	+ (– to ++)	0.041[b]
	Day 10	– (– to +)	+ (+ to ++)	0.026[b]
	Day 14	– (– to +++)	+ (– to +++)	0.818
Medial thickening	Day 5	– (– to –)	+ (– to ++)	0.180
	Day 10	– (– to +)	+ (– to +)	0.394
	Day 14	– (– to –)	– (– to +)	0.699
Advantitial inflation	Day 5	+ (– to +)	+ (– to +)	1.000
	Day 10	+ (– to +)	+ (– to +++)	0.589
	Day 14	+ (– to +)	+ (– to +++)	0.485
Foreign body reaction	Day 5	+ (– to ++)	+ (– to +)	0.485
	Day 10	++ (+ to ++)	+ (– to ++)	0.394
	Day 14	++ (+ to +++)	+ (– to ++)	0.310
Mean luminal diameter (mm)	Day 5	0 (0 to 0.3)	0.45 (0.40 to 0.50)	0.002[b]
	Day 10	0.25 (0.10 to 0.40)	0.40 (0.30 to 0.50)	0.026[b]
	Day 14	0.15 (0 to 0.30)	0.45 (0.40 to 0.50)	0.002[b]

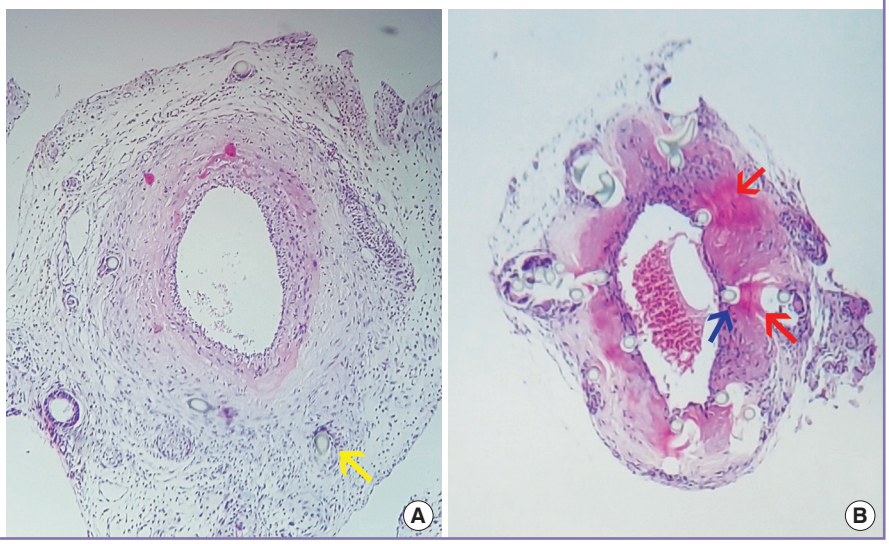
min, minimum; max, maximum.
[a]Mann-Whitney U test; [b]Statistically significant ($P < 0.05$).

thrombosis formation, particularly within 3–5 days following anastomosis. Pseudointima formation also takes place within 5 days. Since permanent endothelium forms on approximately day 14 in rats and the anti-aggregant effects of epigallocatechin gallate peak on day 10, additional histopathological evaluations were performed on day 10 and day 14.

The first striking result of the present study was the significant increase in the mean vessel luminal diameter on day 5 in the epigallocatechin gallate group. This early effect might have stemmed from an early vasorelaxant effect of epigallocatechin gallate on the vessel wall. Early vasorelaxation was also associated with significantly fewer thrombi in the epigallocatechin gallate group.

Fig. 3. Inflammation and foreign body reaction

(A) Reduced inflammation and foreign body reactions around the anastomotic site and increased mean vascular luminal diameter in in the epigallocatechin gallate group (yellow arrow, H&E, ×10). (B) Severe foreign body reactions around the anastomotic site in the control group. Diffuse lymphocytes and multiple giant cells are seen around the microvascular anastomotic site. A blood clot is seen at the center of the lumen. Giant inflammatory cells around the anastomotic site, indicating a severe foreign body reaction (red arrows). Sutures (blue arrow) (H&E, ×10).



Another important finding of this study was the macroscopic color change in the target vessel. The differences in macroscopic color changes between groups were statistically significant on day 10 and trended towards significance throughout the overall study period. This suggests that epigallocatechin gallate leads to less acute bleeding after anastomosis. The trend towards a significant difference in adventitial inflammation between groups is also consistent with the difference in color change. We also found significant differences in thrombus formation on day 5 and in the overall study period. This prompted us to consider the possibility that epigallocatechin gallate facilitated temporary and permanent endothelial formation and reduced early thrombus formation, which may have been mediated by its acute vasorelaxant effect. These findings also suggest that epigallocatechin gallate might be used to prevent thrombus formation, particularly in the early postoperative period, and increase the likelihood of successful microsurgical repair.

However, the small sample size of the study may have reduced the statistical power and prevented some variables from reaching statistical significance. The intimal thickening in the overall study period was significantly different between groups on days 5 and 10 and was supported by a trend towards statistical significance on day 10. Although epigallocatechin gallate was associated with milder foreign body reactions due to its anti-inflammatory effects, the vasorelaxant effect mediated via calcium channels probably contributed to the significantly greater mean vascular luminal diameter in the epigallocatechin gallate group. The mean luminal diameter was larger on days 5, 10, and 14 in the epigallocatechin gallate group, and it was also different between the epigallocatechin gallate and control groups on days 5, 10, and 14, consistent with the vasodilatory effects of epigallocatechin gallate.

Taken together, the histopathological and macroscopic assessments of tissue sections from the microanastomosis site indicate that epigallocatechin gallate improved microsurgical outcomes by providing a smaller thrombus burden, accelerated temporary endothelial formation, marked permanent endothelial formation, reduced inflammation and foreign body reactions around the anastomotic site, and increased mean vascular luminal diameter (Fig. 3). These findings were also supported by hematoxylin and eosin staining.

The available data indicate that epigallocatechin gallate has positive effects on the microcirculation through multiple pathways involving anti-oxidant, vasorelaxant, and anti-aggregant effects. Herein, we have shown that in an experimental model of microvascular arterial anastomosis, administration of epigallocatechin gallate significantly reduced thrombus formation after microvascular repair, particularly in the acute period after surgery. More robust results might be achieved in future large-scale studies, especially if additional methods are incorporated.

Moreover, similar studies on venous anastomoses and random or axial pedunculated skin flaps would also contribute valuable findings relevant to this topic.

NOTES

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Ethical approval

This study was approved by the Ankara University Medical Fac-

ulty Laboratory Animals Ethics Committee (approval No. 53184147-50.04.04/3835).

Author contribution

Study concept and design: İğde M. Data acquisition: Öztürk MO. Data analysis and interpretation: Yaşar B. Drafting of the manuscript: Bulam MH. Critical revision of the manuscript for important intellectual content: Ünlü RE. Statistical analysis: Yaşar B. Administrative, technical, or material support: Ergani HM. Study supervision: İğde M. Approval of final manuscript: all authors.

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