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Twelve-Month Outcomes of a Novel Iopromide-Based Paclitaxel-Coated Balloon for the Treatment of Chronic Total Occlusion of Femoropopliteal Arteries

Femoro-popliteal Arterlerdeki Kronik Total Oklüzyon Tedavisinde İopromid Bazlı Paklitaksel Kaplı Balonun On İki Aylık Sonuçları

ABSTRACT

Objective: We designed a retrospective study to evaluate the performance and outcomes of a novel iopromide-based paclitaxel-coated balloon for the treatment of chronic total occlusion of femoropopliteal arteries.

Materials and Methods: Patients with femoropopliteal chronic total occlusion (<100 mm) on angiogram were screened from hospital management system and were included in the study. The width and length of the drug-eluting peripheral balloon was chosen to ensure a vessel/balloon ratio of 1 : 1 and exceed the lesion by 10 mm on both ends (based on visual estimation).

Results: The proportion of patients with ankle-brachial index improvement was 89.8% (106 of 118). The mean ankle-brachial index was 0.5 (0.4-0.7) at baseline and 0.8 (0.7-0.9) at 12 months ($P < 0.001$). Changes in the Rutherford category between baseline and 12 months were statistically significant ($P < 0.001$), with the majority of patients (77.9%, 92/118) having ≥1 level improvement. The rate of clinically driven target lesion revascularization at 12 months was 13.5% (16/118). Overall, the 1-year primary patency rate was 86.4% (102 of 118). The major adverse limb event rate was 9.8% (16/162). Acute limb ischemia was detected in 14 patients, and amputation was performed in 2 patients.

Conclusion: Our study is a non-randomized clinical study focusing on the use of drug-eluting balloon as a single treatment strategy. There was significant clinical benefit to patients, as clearly demonstrated by the improvement in ankle-brachial index and the reduction in Rutherford class in the short term, and these results may offer clear insights on the revascularization strategy outlook of interventionalists.

Keywords: Angioplasty, ankle-brachial index, chronic total occlusion, coated balloon, interventional cardiology, peripheral arterial disease, Rutherford class

ÖZET

Amaç: Femoro-popliteal arterlerin kronik total oklüzyonunun tedavisi için yeni bir iopromid bazlı paklitaksel kaplı balonun performansını ve sonuçlarını değerlendirmek için retrospektif bir çalışma tasarladık.

Yöntemler: Hastane görüntü kayıt sisteminden alt ekstrimite girişim işlemleri taranarak femoro-popliteal kronik total oklüzyonu (<100 mm) olan hastalar çalışmaya dahil edildi. İlaç salınımlı periferik balonun genişliği ve uzunluğu, 1:1'lik bir damar/balon oranı sağlayan ve lezyonu her iki uçta 10 mm aşacak şekilde yapılan işlemler çalışmaya alındı.

Bulgular: Toplamda 118 hasta çalışmaya alındı. Ankle-brakial indeks iyileşmesi olan hastaların oranı %89.8 saptandı. Ortalama ankle-brakial indeks başlangıçta 0.5 (0.4-0.7) ve 12 ayda 0.8 (0.7-0.9) idi ($P < 0,001$). Başlangıç ile 12 ay arasındaki Rutherford kategorisindeki değişiklikler istatistiksel olarak anlamlıydı ($P < 0,001$) ve hastaların çoğunluğunda (%77.9) bir düzeyden fazla iyileşme vardı. 12 ayda klinik odaklı hedef lezyon revaskülarizasyon oranı %13.5 (16/118) saptandı. Genel olarak, bir yıllık birincil açıklık oranı %86.4 saptandı. Majör ekstremite advers olay oranı %9.8 (16/162) saptandı. 14 hastada akut ekstremite iskemisi saptandı ve 2 hastaya amputasyon uygulandı.

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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Sonuç: Çalışmamız, ilaç kaplı balonların tek bir tedavi stratejisi olarak kullanımına odaklanan, randomize olmayan bir klinik çalışmadır. Kısa vadede ankle-brakial indeks iyileşmesi ve Rutherford sınıfında azalma sağlanmıştır. Çalışma sonuçlarımız revaskülarizasyon stratejisi hakkındaki bakış açımızı değiştirebilecek bilgiler sunabilir.

Anahtar Kelimeler: Ankle-brakial indeks, kronik total oklüzyon, ilaç kaplı balon, periferik arter hastalığı, Rutherford sınıflaması.

Peripheral arterial disease is an important health issue affecting the quality of life and is associated with significant morbidity.[1] Due to the progressing nature of the disease, revascularization is the cornerstone of therapy, necessary to prevent severe complications. The surgical approach yields significant symptomatic improvement and satisfactory long-term results, but the associated high morbidity and mortality preclude its routine use. As an alternative, endovascular treatment methods have been introduced.[2] Drug-eluting balloons (DEBs) present as a promising solution to this challenge. In contrast to an elective stent or surgical revascularization strategy, DEB angioplasty of the femoropopliteal region provides long-term patency without leaving behind prosthetic material or putting the patient under risk of complications. With disease progress within and outside the arterial lesion, DEBs represent an attractive alternative that does not limit future treatment options when compared with any first-line revascularization strategy. It is a treatment modality that allows homogeneous delivery of an antiproliferative drug to the arterial vessel wall.

Addition of paclitaxel led to significantly reduced late lumen loss and restenosis rate in the DEB group when compared with the uncoated balloon group.[3] But the initial high balloon–artery drug transfer rates, very high early drug concentrations in tissue and inconsistent drug coating concentrations, and drug loss during device tracking are several unresolved technical limitations.[4] These reasons may reduce the therapeutic efficacy of the drug released into the arterial wall. To overcome these limitations, a new-generation DEB with iopromide and paclitaxel coating has been developed. Once in contact with blood, the iopromide and paclitaxel coating begins to open, facilitating the pressure-induced transfer of the paclitaxel.[5,6] The properties of iopromide protect the paclitaxel during transition and placement.[7] Although efficacy has been demonstrated in animal experiments, only clinical research will be able to provide information on efficacy and potential safety risks in patients.

On the basis of this background, we designed a retrospective study to evaluate the performance and outcomes of a novel iopromide-based paclitaxel-coated balloon for the treatment of chronic total occlusion (CTO) of femoropopliteal arteries by means of the primary patency rate measured at 12 months. Moreover, the current article will give recommendations for the endovascular treatment of femoropopliteal arteries.

Materials and Methods

Study Design

This is a single-center retrospective clinical study assessing the safety and effectiveness of the paclitaxel-coated balloon with iopromide as an excipient balloon for the treatment of real-world patients with CTO of femoropopliteal arteries. Patients with chronic extremity ischemia and with totally occluded femoropopliteal vessels on angiography were included. The study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines and was approved by the local Institutional Review Board. Local Ethics Committee approved the study (date: 25.01.22 and no.: 2022.09.01.09).

Endpoints and Definitions

Major adverse limb events were defined as the composite of acute limb ischemia and amputation. Major adverse cardiovascular events included myocardial infarction, stroke, and cardiovascular death. The primary outcome was freedom from binary restenosis, as determined by >50% stenosis on digital angiography or arterial systolic peak velocity ratio ≥ 2.4 on Doppler ultrasound during 12 months follow-up. Secondary endpoints included any target lesion revascularization, any target limb revascularization, and major adverse events (all-cause mortality, major target limb amputation, and thrombosis at the target lesion site) evaluated at 12 months.

Patient Population

Patients with femoropopliteal CTO (≤100 mm) on digital subtraction angiography were screened from hospital management system and were included in the study. Rutherford class and ankle-brachial index (ABI) (relationship between systolic blood pressure in the ankle and brachial artery) records were noted.[8,9] Angiographic inclusion criteria included occlusions for a total length of ≤100 mm by radiopaque ruler estimate. Patients with nonocclusive SFA-popliteal arterial obstruction, angiographically evident thrombus, prior ballooning/stenting, and priorly peripheral vascular operation history were excluded. Patients who developed gross dissection, rupture, and stent implantation during the procedure were excluded.

To assess the grade of calcium, to prevent unnecessary interventions, and to determine detailed anatomy, we use computed tomography before digital subtraction angiography for all patients. The arterial vasculature obtained from computed tomography was read by 1 experienced cardiologist to categorize the femoropopliteal occlusions. Total occlusion length from the beginning of the occlusion up to the recovery was included in the measurement. The mean diameter of the occluded segment, obtained by the averaging of at least 2 manual measurements on transverse cross-sections, was used. We measured calcium extension both circumferentially and longitudinally. Circumferential grade was measured by assessing the presence of calcium in 1 or more of the 4 90° sectors. Severely calcified lesions were defined as circumference ≥180° on both sides of the vessel at the same location and lengths greater than half of the total lesion length.

We recommend endovascular intervention first for short (<25 cm) lesions. The intervention decision was made only after a failed optimal medical treatment for our patients with

claudication.[9-15] Our main goal in endovascular intervention is functional improvement, taking into account the potential for improvement in quality of life or exercise rehabilitation rather than relying solely on the presence of a stenotic lesion or the extent of anatomical involvement. The severity of the patient's injury (painless walking distance and maximum walking distance) and how much this affects their daily activities are investigated.

Patients returned for follow-up at first, sixth, and twelfth months for physical examination. All assessments including clinical examination, Rutherford classifications, and ABI measurements were performed before hospital discharge and at every follow-up visit during the first year (Figure 1).

In our clinic, an experienced ultrasonographer performs duplex ultrasound studies with 5 MHz linear-array transducers for the determination of patency and orders computerized tomography angiography or digital subtraction angiography evaluation when arterial restenosis was suspected. We emphasize lifestyle modifications for risk reduction, including smoking cessation, antiplatelet therapy, and hypercholesterolemia control during the follow-up visits.

Angioplasty Technique

Twelve hours before the procedure, patients received loading doses of aspirin and clopidogrel. We used retrograde approach for all patients via the ipsilateral popliteal artery. Popliteal puncture was done under ultrasound guidance. Local anesthesia was injected, followed by puncturing the popliteal artery. Puncture was made in the popliteal area using a needle inserted to form an angle of 45° with the skin surface. We used introducer sheaths ranging from 6F to 7F which were placed into the popliteal artery using the Seldinger technique. Patients received a bolus of heparin (80-100 U/kg) after the insertion of the introducer sheath.

The popliteal and superficial femoral arteries were visualized via an angiogram. Retrograde subintimal recanalization of occlusions was performed using a 0.035-inch stiff hydrophilic guidewire (Invamed, Inwire Guidewire) and catheter (Invamed, Dolphin Zebra Crossing Support Catheter, Ankara, Türkiye) support. Re-entry was confirmed by injection of contrast. In 12 patients, an above and below approach was required, and the intervention was completed by removing the wire from the sheath above. An intraluminal or subintimal approach, or a combination of the 2, was used to bypass chronic total lesions. When the wire re-enters the distal lumen, a catheter is advanced over the wire into the distal lumen, and a contrast is injected to confirm the distal intraluminal position of the catheter. Then, a working wire is placed, and the core was treated over this wire. After successful lesion crossing, the entire subintimal space was dilated with a balloon catheter. Resistant stenoses were redilated with a 1-mm larger balloon. The target lesion was first treated with standard uncoated balloons and then with drug-coated balloons, provided there was no residual stenosis or dissection after standard balloon angioplasty. Extender DEB (RD Global-Invamed, Ankara, Turkey) was used to reduce intimal hyperplasia. This is an iopromide-based paclitaxel-coated balloon designed for femoropopliteal lesions. The width and length of the balloon was chosen to ensure a vessel/balloon ratio of 1 : 1 and exceed the lesion by 10 mm on both ends. To ensure homogenous and complete drug release, balloons were kept inflated for 3 minutes at 4-12 atm. Procedural success was defined as residual stenosis ≤30% by laboratory assessment. This analysis is lesion based. Lesions considered procedural successful were included in the study. Control arteriography was done at the end of the procedure for assessment of success and potential complications. Post-procedure patients were prescribed aspirin to be taken indefinitely and clopidogrel daily for 12 weeks.[15]

Figure 1. Measurement of ABI. Measuring of the ABI was performed by measuring the systolic blood pressure from both brachial arteries and from the dorsalis pedis on the side of occlusion after the patient has been at rest in the supine position for 10 minutes. The systolic pressure was recorded with a handheld Doppler instrument. The ABI value was determined by taking the pressure of the arteries on the side of occlusion divided by the brachial arterial systolic pressure. The higher of the 2 brachial systolic pressure measurements was used. ABI, ankle-brachial index.

Statistical Analyses

Statistical analyses were performed using the Statistical Package for Social Sciences software version 18. Descriptive statistics were expressed as numbers and percentages for categorical variables and as mean, SD, median, quartiles, and range for numerical variables. For categorical variables, the chi-square test was used in 2 independent groups and multiple comparisons and Fisher's exact test were used when the chi-square condition was not met. The Student's *t*-test was used for continuous data conforming to the normal distribution for independent groups. The Mann–Whitney *U*-test was used for non-normally distributed data for independent groups. In comparison of 2 dependent groups, the Wilcoxon signed-rank test was used for non-normally distributed numerical variables. A *P*-value of less than 0.05 was considered statistically significant.

Results

Patient Characteristics

The data of 380 patients with performed peripheral angiography procedure registered in the hospital imaging system were analyzed from October 2017 to January 2021 retrospectively. Two hundred seventy patients were revascularized using the iopromide-based paclitaxel-coated balloon, and 192 of 270 patients were revascularized for femoropopliteal CTO. Patients who needed stent implantation (n=39) and who developed rupture (n=1) during the procedure were excluded. The technical success was 79% after paclitaxel-coated balloon treatment and 99.4% after paclitaxel-coated balloon plus stent implantations. Patients with technical success after the drug-coated balloon procedure were included in the study (n=152). Thirty-four patients were excluded from the study because of irregular clinic follow-up. Finally, 118 patients and 162 arteries were included in the study. Of these patients, 68 were male and 50 were female, and the mean age was 66.3 ± 9.6 years. Of all the patients, 32.2% of patients had diabetes mellitus, 74.6% had coronary artery disease, and 13.4% had chronic kidney disease. Thromboembolic risk and bleeding risks were calculated before endovascular intervention in our patients using warfarin (n=4), dabigatran (n=1), rivaroxaban (n=4), and apixaban (n=3). Bridging anticoagulatıon was appropriated in 5 patients.

The mean lesion length was 73.2 ± 18.2 mm. The mean DEB diameter was 5.96 ± 1.4 mm and length was 94.4 ± 5.3 mm. The majority (83.3%) of lesions were calcified, and 39.5% were severely calcified. The median baseline Rutherford class was 3 (2.0-5.0). The median follow-up was 12.8 months (Table 1).

Table 1. Baseline Clinical Characteristics of Patient and Initial Lesion Characteristics

Variables	Results
Clinical characteristics	
Age, years, mean ± SD	66.3 ± 9.6
Gender, n (%), male	68 (57)
Hyperlipidemia, n (%)	38 (32)
Hypertension, n (%)	84 (71)
Coronary artery disease, n (%)	88 (74)
Carotid artery disease, n (%)	34 (28)
Current smoker, n (%)	70 (59)
Type-2 diabetes mellitus, n (%)	38 (32)
Obesity (body mass index ≥30 kg/m^2), n (%)	28 (23)
Ankle-brachial index, median	0.5 (0.4-0.7)
Rutherford category, n (%)	
0	0
1	0
2	31 (26)
3	48 (40)
4	28 (23)
5	11 (9)
6	0
Angiographic characteristics	
Superficial femoral artery, n (%)	92 (56)
Proximal superficial femoral artery	19 (11)
Mid-superficial femoral artery	31 (19)
Distal superficial femoral artery	42 (25)
Popliteal artery, n (%)	18 (11)
Both superficial femoral and popliteal artery, n (%)	52 (32)
Calcification, n (%)	135 (83)
Severe calcification, n (%)	64 (39)
Target lesion length, mm	73.2 ± 18.2
Reference vessel diameter, mm	59.0 ± 8.0
Lesion type	
De novo	162 (100)
Restenotic	0

Efficacy and Functional Outcomes

When the pre-intervention and pre-hospital discharge (post-intervention) examination findings were compared, ABI had significantly decreased ($P < 0.05$) and Rutherford had significantly decreased ($P < 0.05$). The proportion of patients with ABI improvement was 89.8% (106 of 118). The mean ABI was 0.5 (0.4-0.7) at baseline and 0.8 (0.7-0.9) at 12 months ($P < 0.001$). Changes in the Rutherford category between baseline and 12 months were statistically significant ($P < 0.001$), with the majority of patients (77.9%, 92/118) having ≥1 level improvement (Table 2).

The decisions for revascularization were made according to the patient's clinical complaints. The rate of clinically driven target lesion revascularization at 12 months was 9.8% (16/162). The mean time to first clinically driven target lesion revascularization was 8.4 ± 3.2 months. Fourteen restenosis occurred in a total of 16 patients. Fourteen of 16 patients were revascularized with the diagnosis of acute limb ischemia and 2 of 16 patients with the diagnosis of claudication. In patients with acute limb ischemia, coexistence of restenosis and thrombosis was found in

Table 2. Initial and Latest Ankle-Brachial Index and Rutherford Classifications of Patients

	Initial	Latest	*P*
Ankle-brachial index, median	0.5 (0.4-0.7)	0.8 (0.7-0.9)	<0.001
Rutherford classifications, median	3.0 (2.0-5.0)	2.0 (2.0-3.0)	<0.001

11 (1 patient amputated due to non-healing wounds), embolism in 2 (1 patient had coexistence of restenosis and embolism and 1 patient amputated due to gangrene of the foot), and thrombosed popliteal aneurysm in 1 patient. Restenosis was detected in 2 patients with claudication and number of asymptomatic restenosis was 1 (Table 3). Overall, the 1-year primary patency rate was 88.2% (143/162). The patients were divided into 2 groups according to the Rutherford classification. Rutherford class 2-3 was defined as moderate or severe claudication, and Rutherford class 4-5 was defined as ischemic rest pain or minor tissue loss or focal gangrene. The subgroups stratified by baseline clinical characteristics found that patients with Rutherford class 2-3 had significantly lower 12-month freedom from clinically driven target lesion revascularization compared to patients with Rutherford class 4-5 (98% and 72%; respectively).

Safety Outcomes

Nine patients developed local hematoma after the procedure, which could be treated with compression. Acute limb ischemia was detected in 14 patients, and amputation was performed in 2 patients. The most common causes for acute limb ischemia were combination of thrombosis and restenosis. Two patients were amputated due to non-healing wounds and gangrene extending into the deep tissues of the foot. Both patients had extensive femoropopliteal occlusive disease with aorto-iliac and distal infra-popliteal lesions.

Table 3. Twelve-Month Outcomes in 118 Patients

Outcomes	Summaries
Major adverse events—composite	
Death (all cause)	4% (5/118)
Target lesion revascularization	9% (16/162)
Major target limb amputation	1% (2/118)
Asymptomatic restenosis	0.6% (1/162)
Claudication with restenosis	1.2% (2/162)
Acute limb ischemia	8.6% (14/162)
Embolization	1% (2/162)
Thrombosis and restenosis	6.7% (11/162)
Thrombosed popliteal aneurysm	0.6% (1/162)
Primary patency rate	88.2% (143/162)
Ankle-brachial index improvement	89.8% (106/118)
Rutherford category improvement	77.9 % (92/118)
Twelve-month freedom from target lesion revascularization	
Rutherford category 2-3	98% (78/79)
Rutherford category 4-5	72% (28/39)

The 1-year major amputation rate in patients with Rutherford Class 2-3 was 1.2% (1/79) compared with 2.5% (1/39) for patients with Rutherford Class 4-5 ($P=0.015$). But the all-cause mortality was 4.2% (5/118) through 12 months. Cardiovascular (n=3), malignancy (n=1), and infection/inflammatory (n=1) diseases were the causes of five deaths (Table 3).

Discussion

The results of this registry demonstrate that iopromide-based paclitaxel-coated balloon angioplasty for the treatment of the totally occluded femoropopliteal arteries has been found to provide satisfactory patency rates with favorable results on the Rutherford class and ABI over a 12-month period. All of the lesions included in the study were totally occluded lesions. The difference between our study from previous studies was that our study included a significant number of patients and investigated the results of iopromide-based paclitaxel-coated balloons in total femoropopliteal lesions. The present study was conducted in a group of patients with typical routine clinical practice. The balloon we used is covered with a surface coating that allows the paclitaxel to penetrate more evenly into the tissue; these technological features have contributed to satisfactory target lesion revascularization rates in all clinical conditions. In this registry, the use of the novel iopromide-based paclitaxel-coated balloon for the treatment of femoral-popliteal total occlusions was shown to be valuable at the end of the twelve months. An important clinical outcome from this study was the improvement in Rutherford classification in patients with critical lower extremity ischemia in the registry, thus emphasizing the need to improve clinical and interventional care in these patients.

Drug coating of the balloons significantly improved the long-term outcomes of angioplasty.[17] The coatings of the balloons are different from each other. The use of "real-world" recordings can help provide an assessment of the safety and efficacy of a new lined balloon in daily clinical practice. The paclitaxel-eluting balloons differ in the excipients added (iopromide, urea, sorbitol, citric acid ester, dextran, polyethylene glycol, and butyryl trihexyl citrate).[18,19] Technological advances in excipients aim for minimization of drug loss and optimization of drug absorption in the vessel wall.[7,20]

In DEBATE trial (Drug-Eluting Balloon in Peripheral Intervention for the Superficial Femoral Artery), DEBs showed a significant reduction in restenosis recurrence when compared with plain old balloon angioplasty.[21] While the TLR rate was 13.6% and restenosis rate was 13% in the DEB+bare metal stent (BMS) subgroup in the DEBATE study, the target lesion revascularization (TLR) rate was 9.8% and restenosis rate was 10.4% in our study. Patients with critical limb ischemia were not included in our patient population. In addition, patients who developed flow-limiting dissection and recoil during the procedure were not included in our study.This may be the reason why our TLR and restenosis rates were found to be slightly lower than those of the DEBATE study. According to this result, if dissection or restenosis did not develop during the procedure, it may be reasonable to stay away from routine stenting after DEBs. IN.PACT Global Study is the

prospective multicenter clinical trial evaluating urea-based paclitaxel-coated balloon for the treatment of femoropopliteal CTO.[22] In the paclitaxel-coated balloon group (mean length of 228.3 ± 97.6 mm), primary patency at 12 months was 82.7%. In our study, the 12-month primary patency rate was higher (88.2%); however, the mean lesion length was shorter (73.2 ± 18.2 mm).

The challenging idea behind the drug-coated balloon concept is the biological modification of the injury response after balloon dilation. Antiproliferative drugs administered via drug-coated balloons suppress neointimal hyperplasia and restenosis.[19] Conversely, long-term suppressed intimal healing may cause thrombus formation. The 12-month incidence of thrombosis at the target lesion occurred in 4.3% (5 of 115) of all subjects in the results of IN.PACT study. In our study, 14 of 118 patients presented with acute limb ischemia and thrombosis were found in 11 patients. Our thrombosis rate was 9.3%. Increase of thrombosis may be a considerable question mark after DEBs.

Limitations

In the absence of an active comparator, the results of this study cannot support direct comparison to other endovascular treatment options. Evaluation of iopromide-based paclitaxel-coated balloon effectiveness was limited to clinical outcomes in our study. Only patients with CTO were included in our study. We determined the effects of DEBs for the treatment of femoropopliteal in the presence of CTO. According to a previous study, non-CTO patients showed a significantly better clinical primary patency than CTO patients after balloon.[23] Some studies were underpowered to sufficiently discriminate the efficacy of balloons in patients with CTO and without CTO.[24] The presence of CTO should be considered when selecting a balloon to be used in endovascular interventions of femora-popliteal lesions. Confounding variables such as the presence of CTO reduce the ability to make causal inferences between intervention and outcomes. To decrease the impact of confounding variables, we used restriction and included only patients with CTO.

Conclusion

Our study is a non-randomized clinical study focusing on use of DEBs as a single treatment strategy. In addition, we could not find a record of the lengths of revascularized arterial segments that would be a reason for worse outcomes of DEBs. However, there was significant clinical benefit, demonstrated by the improvement in ABI and the reduction in Rutherford class in the short term. The current study also presents the results, efficacy, and safety of DEBs in femoropopliteal arteries of patients with similar basic characteristics.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Tekirdağ Namık Kemal University (Approval No: 2022.09.01.09).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

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