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ORIGINAL ARTICLE

# Effect of a mixture of diosmin, coumarin glycosides, and triterpenes on bleeding, thrombosis, and pain after stapled anopexy: a prospective, randomized, placebo-controlled clinical trial

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**Abstract**
*Purpose* We evaluated the efficacy of oral administration of a mixture of diosmin, coumarin glycosides, and *Centella asiatica* (Venoplant®) in preventing bleeding, pain, and thrombosis of internal and external hemorrhoids after stapled anopexy (SA).
*Methods* SA was conducted in 182 patients with third-degree hemorrhoids. Preoperatively, patients were randomized evenly into two groups. Group A patients were administered Venoplant for 30 days post-SA, and group B received a placebo for 30 days post-SA. Patients received paracetamol for postoperative pain. Visit (v)1, v2, and v3 took place 7, 15, and 30 days postoperatively, respectively; bleeding (clinical examination), visual analog scale (VAS), thrombosis (clinical examination), and pain (paracetamol dosage, VAS) were evaluated.
*Results* At v1, v2, and v3, the numbers of patients with bleeding in groups A and B were 21 and 46, 3 and 25, and 1 and 5, respectively ($p < 0.05$). At v1, v2, and v3, the numbers of patients in groups A and B with thrombosed internal hemorrhoids were 3 and 13, 2 and 11, and 1 and 8, respectively ($p < 0.05$). The number of patients who took at least one paracetamol tablet was similar in both groups at v1 but was significantly greater in group B than group A at v2 and v3 ($p < 0.05$); pain VAS scores were equivalent at v1 and significantly greater in group B than group A at v2 and v3 ($p < 0.05$).
*Conclusions* Venoplant effectively reduced bleeding after SA, decreased the incidence of thrombosed internal hemorrhoids, and decreased postoperative pain.

**Keywords** Stapled anopexy · Complications · Venoplant · Bleeding · Pain · Thrombosis

## Introduction

In 1993, stapled anopexy (SA) was proposed as an alternative method for surgical management of hemorrhoids [1]. SA reduces the size of internal hemorrhoids by interrupting their blood supply, thereby reducing the amount of rectal mucosa that can prolapse. Several complications can occur in the first 7 days after surgery: bleeding (prevalence, 0–68%), thrombosis of internal hemorrhoids (TH; 5.5% [2]), and thrombosis of external hemorrhoids (TEH; 0–13% [3]). These complications are usually treated conservatively; only a limited number of cases experience postoperative bleeding causing severe anemia that necessitates new surgical intervention. In addition, postoperative pain has been reported in 24% of patients undergoing SA [4].

Patients with grade I or II hemorrhoids, for which surgical management is not recommended, are generally administered medications containing micronized purified flavonoid fraction (MPFF) [5, 6]. Studies on the efficacy of MPFF for the treatment of early postoperative complications of hemorrhoid management have contained controversial and incomplete

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data. Several studies have reported that flavonoids can reduce the incidence of postoperative bleeding [7, 8], but there is no evidence that these compounds have an effect on postoperative pain and thrombosis [5].

*Melilotus officinalis* is a species of legume that contains coumarin and has pro-lymphokinetic and proteolytic actions. Coumarin reduces edema and inflammation in tissues and leads to an improvement in capillary permeability [9]; however, the mechanisms underlying its pharmacologic activity are not known. It may be possible to increase the beneficial therapeutic effect of coumarin by using it in combination with other compounds [9].

*Centella asiatica* is a small, herbaceous, frost-tender, perennial plant that reduces endothelial permeability and capillary filtration. Capillaroscopy has shown that *C. asiatica* affects microcirculation and inhibits inflammation [10, 11].

The aim of the present study was to evaluate the efficacy of oral administration of a mixture of diosmin, coumarin glycosides, and *C. asiatica* (Venoplant®; Aesculapius, Brescia, Italy) in prevention of bleeding, pain, TH, and TEH in patients who have undergone SA.

## Patients and methods

The study protocol was approved by the local ethics committee. All patients provided written informed consent to participate in this randomized, prospective trial.

### Study cohort

A total of 182 patients who underwent SA for third-degree hemorrhoids in colorectal units in two hospitals in Italy (S. Maria dei Battuti Hospital and S. Valentino Hospital) from 1 June 2014 to 31 January 2016 were enrolled in this study. Preoperatively, patients were allocated randomly into either group A or group B using GraphPad (San Diego, CA, USA). To minimize the risk of predicting the treatment assignment of the next eligible patient, randomization was performed in permuted blocks of two, with random variation of the blocking number, to create a randomization table. The randomization number was placed on the outside of an envelope, with the group assignment sealed inside the envelope. When the patient was enrolled, the envelope was opened to reveal the group assignment. The treatment allocation was blinded for patients, investigators, and the statistician.

### Inclusion and exclusion criteria

Patients were eligible for inclusion in this study if preoperative proctological examination indicated that they had third-degree hemorrhoids according to the Goligher classification [12]. No patients had preexisting medical conditions or were taking medications that would affect their ability to undergo surgery. Exclusion criteria were treatment with oral anti-coagulant and anti-platelet agents, coagulation disorders, and history of radiotherapy in the pelvic/perineal areas.

### Patient groups and treatment

During preoperative examination (v0), patients underwent clinical and proctologic evaluation. The proctological assessment included inspection of the perianal area for the presence of fistula-in-ano, anal fissure, and perianal dermatitis; digital examination and anoscopy were conducted with the patient in the left lateral position. The nature and duration of symptoms and severity of hemorrhoid disease according to the Goligher classification were recorded [12].

All patients had SA conducted by two surgeons using a 33-mm circular stapler. The intervention was carried out as day surgery, and all patients spent one night in hospital. Group A patients ($n = 91$) were treated with Venoplant (one tablet, three times daily (t.d.s.)) for 30 days from the day of surgery; each Venoplant tablet contained the active substances diosmin (300 mg), coumarin (32 mg), and triterpenes in *C. asiatica* at 45% (15 mg). Control patients (group B, $n = 91$) received placebo treatment (one tablet, t.d.s.) for 30 days from the day of surgery; each placebo tablet contained only excipients. All patients in both groups were prescribed a fiber-rich diet with a bulking agent supplement (*Psyllium plantago*). Paracetamol (500 mg, p.o.) was offered to all patients for postoperative pain management; the number of tablets taken was used to assess pain severity. Patients were asked to report symptoms and medications used for treatment of postoperative pain in a diary. Patients and clinical staff were blinded to the study protocol.

Three follow-up examinations were conducted: visit (v)1, v2, and v3, which were conducted 7, 15, and 30 days after surgery, respectively. During each examination, bleeding, thrombosis, and pain were evaluated, and the information reported in the patient's clinical diary was analyzed and discussed. Bleeding was verified by proctological examination, including digital examination and anoscopy, and subjective evaluation (visual analog scale (VAS), where 0 = no bleeding and 10 = hemorrhage). Thrombosis of hemorrhoids was investigated only by proctological assessment. Another VAS was used to quantify pain intensity (where 0 = no pain and 10 = the worst pain imaginable). All patients were followed up from v1 until the end of the study (v3). Each clinician reported patient data in a dedicated database.

### Statistical analyses

Statistical analyses were all performed by the same operator, who was blinded to the study protocol. Data were analyzed using GraphPad. Results are presented as the mean ± SD.

One-way analysis of variance (ANOVA) followed by post hoc Bonferroni's multiple comparison test was carried out to compare variation of patient characteristics before treatment; $p < 0.05$ was considered significant. The chi-squared test was used to analyze the differences between group A and group B with respect to bleeding and thrombosis of hemorrhoids; $p < 0.001$ was considered significant. The ANOVA Fisher *f* test was done to evaluate differences in postoperative pain between groups; $p < 0.05$ was considered significant. Percentage variations were analyzed using Fisher's exact test.

## Results

In total, 182 patients who underwent SA for third-degree hemorrhoids were enrolled (100 males, 82 females; mean age 52.04 ± 11.69 years, range 31–74 years; Table 1). There were no significant differences between groups A and B in sex and age distribution. Group A included 91 patients (49 males, 42 females; mean age 52.44 ± 11.62 years, range 31–73 years), and group B included 91 patients (51 males, 40 females; mean age 51.64 ± 11.80 years, range 31–74 years).

Complications during the first 24 h were fecal urgency in 26 patients in group A (28%) and 28 in group B (30%). Urinary retention was observed in five patients in group A (5%) and four in group B (4%); seven patients required temporary catheterization. Intraoperative technical difficulty in sheath placement resulted in superficial anal fissure in one patient in group A and two in group B; this was managed by stool softeners. Postoperative bleeding was scarce in both groups; this was managed conservatively and did not cause anemia. No wound dehiscence was noted during digital examination. During follow-up, pruritus was experienced by three patients in group A (3%) and two in group B (2%). There were no severe complications necessitating re-intervention and/or rehospitalization. There were no dropouts and/or adverse reactions due to administration of Venoplant or placebo.

### Visit 1

Bleeding was clinically evident in significantly less patients in group A (21 of 91 patients, 23%) than in group B (45 of 91 patients, 49%; $p < 0.05$; Fig. 1). VAS estimation of bleeding confirmed the clinical evaluation, as there was a significant reduction in VAS score reported by group A compared with group B ($p < 0.05$; Fig. 2).

TH was detected significantly less often in group A ($n = 3$) than in group B ($n = 13$; $p < 0.05$; Fig. 3). Three patients from group B and none from group A were affected by TEH. Mean VAS score for pain at v1 tended to be lower in group A (3.6 ± 1.6) than in group B (4.1 ± 1.7), although this difference was not significant ($p = 0.75$; Fig. 4). There was no significant difference between the two groups in paracetamol administration.

### Visit 2 and visit 3

At v2, bleeding was less prevalent in group A ($n = 3$) than in group B ($n = 25$; $p < 0.005$). At v3, bleeding was present in only one patient in group A and five in group B ($p < 0.05$; Table 2).

At v2, there was a significantly lower incidence of TH in group A ($n = 2$) than in group B ($n = 11$; $p < 0.05$). At v3, TH was present in only one patient in group A and eight in group B ($p < 0.05$; Table 3).

There was no significant difference in the incidence of TEH between groups at v2 or v3. TEH was detected in one patient in group A and three in group B at v2; at v3, only one patient in group B had TEH.

At v2, the mean VAS score for pain was significantly lower in group A (1.03 ± 1.6) than in group B (2.06 ± 1.9; $p < 0.05$). At v3, the mean VAS score for pain was again significantly

**Table 1** Demographic characteristics of patients undergoing stapled anopexy

| | Group A | Group B | *P* values |
|---|---|---|---|
| Males/females | 49/42 | 51/40 | ns[b] |
| Age (years) | 52.44 (range, 31–73) | 51.64 (range, 31–74) | ns[b] |
| Symptom duration (months) | 28.95 (range, 10–80) | 29.31 (range, 10–61) | ns[b] |
| Grade of hemorrhoids[a] | 81 (89%) | 79 (86%) | ns[b] |
| 3 | 10 (10%) | 12 (13%) | ns[b] |
| 4 | | | ns[b] |

*Group A* patients administered Venoplant for 30 days after stapled anopexy, *Group B* patients administered placebo for 30 days after stapled anopexy, *ns* not significant ($p > 0.05$)

[a] Goligher's classification

[b] One-way analysis of variance with Bonferroni's multiple comparison test

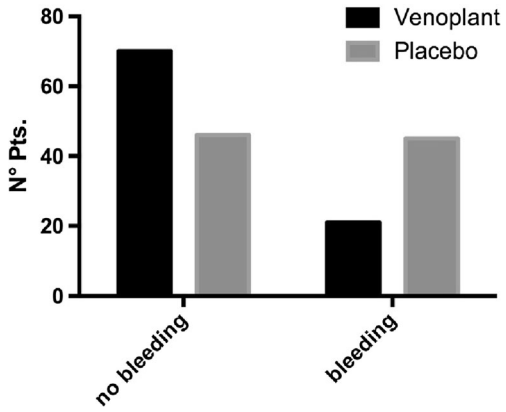


**Fig. 1** Bleeding as evidenced by proctologic examination at visit 1

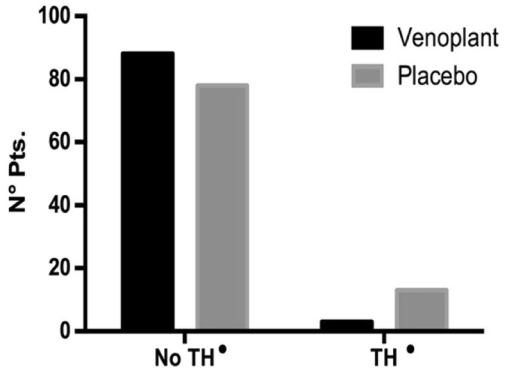


**Fig. 3** Patients with thrombosis of internal hemorrhoids at visit 1. *TH* thrombosed internal hemorrhoids

lower in group A (0.1 ± 0.59) than in group B (0.3 ± 0.6; $p < 0.05$; Fig. 5). The number of patients requiring ≥500 mg/day of paracetamol for management of postoperative pain was significantly lower in group A than in group B at v2 and v3 (both $p < 0.05$; Table 4, Fig. 5).

## Discussion

The pathogenic mechanism of hemorrhoid disease is incompletely understood. However, the alteration of muscles and ligaments and the laxity of anal submucosae are well-recognized pathogenic elements, as they result in venous dilatation; this phenomenon is known as vascular thrombosis, a degenerative process of collagen fibers and further distortion of support structures [13]. Another important pathophysiologic change in hemorrhoid tissue is increased microvascular density, especially when there are increased levels of vascular endothelial growth factor. In a morphologic study, Aigner et al. observed a larger diameter, greater blood flow, and a higher peak and acceleration velocity in the superior rectal artery in hemorrhoid cases [14]. Increased caliber and blood flow in arteries are closely correlated with hemorrhoid grade [14].

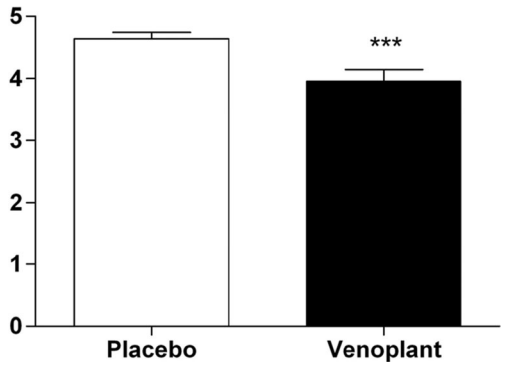


**Fig. 2** Bleeding (VAS score) at visit 1

Hemorrhoids are painful, time-consuming, and expensive complications, which may potentially be prevented by oral supplementation with *C. asiatica* and flavonoids. These supplements could enhance the integrity of connective tissue, increase levels of the anti-oxidants involved in wound healing, and improve capillary permeability [15, 16].

Diosmin is a flavonoid used to improve the tone of venous vessels, reduce excessive microvascular permeability, and reduce edema [7, 17]. Cospite reported that MPFF administration significantly reduced the prevalence of anal bleeding, edema, congestion and pain and that use of analgesics and duration of anal bleeding were diminished [15].

*M. officinalis* extracts are particularly rich in coumarin glycosides, of which 0.4–0.9% is transformed into coumarin. Coumarin has anti-edema and anti-inflammatory properties, as it suppresses phosphorylation of protein kinase B16 [18]. Coumarin in sweet clover stimulates the action of proteolytic enzymes in macrophages, which are the main cause of edema [19].

*C. asiatica* contains triterpene glycosides (e.g., centella saponin, asiaticoside, madecassoside, and sceffoleoside [20]), asiatic acid, madecassic acid, and flavonoids [21, 22]. *C. asiatica* compounds exhibit a broad spectrum of therapeutic activity, the most important of which are anti-oxidant and anti-inflammatory. *C. asiatica* has effects on metabolism in the connective tissue of vascular walls and on microcirculation [23]. This compound reduces edema, controls the capillary filtration rate, and improves microcirculatory parameters and microvascular permeability [20], and its effects are dose dependent [24, 25]. These effects of *C. asiatica* on the microcirculation could be useful for treatment of bleeding hemorrhoids [26].

Some studies have revealed the benefits of micronized flavonoids after hemorrhoidectomy, especially for reducing bleeding and symptoms after hemorrhoidectomy, but not for postoperative pain or TEH [5, 7, 8]. Mlakar et al. investigated the role of MPFF after SA but could not demonstrate positive effects using flavonoids [27]. Therefore, the aim of our study

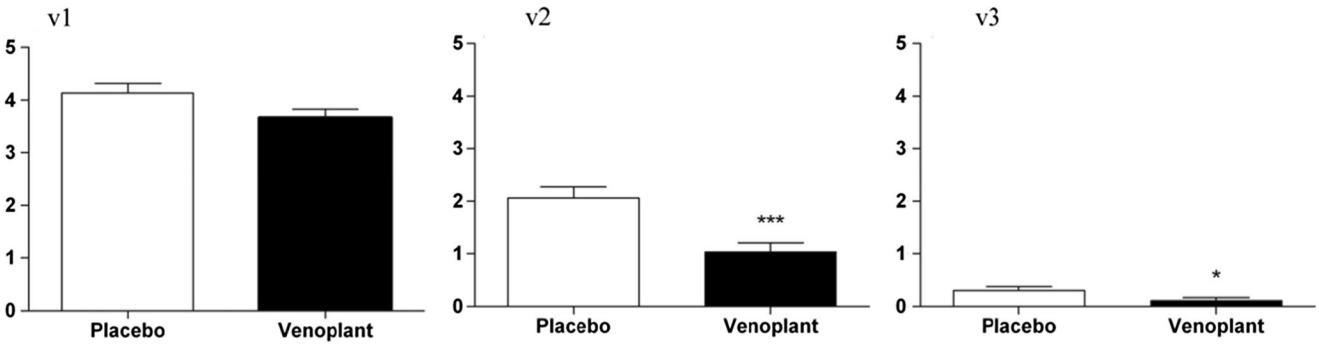


**Fig. 4** Pain (VAS score) at visit 1, visit 2 and visit 3. ANOVA Fisher *f* test

was to determine if a mixture of diosmin, coumarin glycosides, and triterpenes could prevent anal bleeding, TH, and pain after SA.

Bleeding is considered the most common complication after SA, but with a lower prevalence than after other methods of hemorrhoidectomy. Bleeding has been reported to occur immediately or from day 7 onward, with an overall prevalence after hemorrhoidectomy of 0–68% [2, 7]. Perera et al. reported a significant benefit of using phlebotonics in treating bleeding post-hemorrhoidectomy [5]. Similarly, the present results suggested that Venoplant was efficacious in the management of postoperative bleeding, especially during the first 2 weeks postoperatively; Venoplant was less effective 15–30 days after SA. Bleeding was detected in the proctological assessment in significantly less patients treated with Venoplant than in the control group. Patient evaluation of bleeding intensity using a VAS scale confirmed our observations. Reduction of bleeding caused by Venoplant administration was also associated with faster recovery after SA. None of our patients suffered severe bleeding or clinically relevant anemia.

TH has been reported as an early and late painful complication after SA, with a prevalence of 1–13% [2, 3]. In the present study, the prevalence of TH was significantly lower in Venoplant-treated patients than in patients treated with placebo. This was probably due to the anti-edema activity of coumarin, which has activity against the colloid osmotic pressure involved in edema formation [28]. Coumarin causes activation of macrophages and other circulating immune cells, which can produce proteolytic enzymes. The latter transform the proteins present in the perivascular interstitium into small molecular fragments, which can be readily drained from this site [28, 29]. Coumarins and flavonoids have been shown to have anti-inflammatory properties and to interact with several enzymes [30].

Pain is a frequently occurring complication after hemorrhoidectomy [31]. Pain was significantly lower in Venoplant-treated patients than in the control group; there was no statistical evidence for the ability of Venoplant to reduce immediate postoperative pain (v1), but Venoplant-treated patients had a lower pain VAS score overall. At v2 and v3, pain was significantly lower (according to VAS score) in the Venoplant-treated group than in the control group.

Our study had two main limitations. First, we did not have a group of patients who were administered flavonoids alone. Second, the small number of patients treated with Venoplant limited the strength of statistical analyses. Conversely, the major strengths of our study were its prospective nature and the standardization of data collection.

## Cost data

It is necessary to assess the cost-effectiveness of therapy, especially when evaluating a new therapy involving additional

**Table 2** Number of stapled anopexy patients who experienced bleeding at visit (v)1, v2, and v3

| Scheduled visit | Group A | Group B | *P* values |
|---|---|---|---|
| v1 | 21 | 46 | <0.05[a] |
| v2 | 3 | 25 | <0.05[a] |
| v3 | 1 | 5 | <0.05[a] |

Bleeding was detected via proctologic examination

*Group A* patients administered Venoplant for 30 days after stapled anopexy (SA), *Group B* patients administered placebo for 30 days after SA, *v1* 7 days post-SA, *v2* 15 days post-SA, *v3* 30 days post-SA

[a] ANOVA Fisher *f* test

**Table 3** Number of stapled anopexy patients with thrombosed internal hemorrhoids at visit (v)1, v2, and v3

| Scheduled visit | Group A | Group B | *P* values |
|---|---|---|---|
| v1 | 3 | 13 | <0.05[a] |
| v2 | 2 | 11 | <0.05[a] |
| v3 | 1 | 8 | <0.05[a] |

Thrombosed internal hemorrhoids were detected via proctologic examination

*Group A* patients administered Venoplant for 30 days after stapled anopexy (SA), *Group B* patients administered placebo for 30 days after SA, *v1* 7 days post-SA, *v2* 15 days post-SA, *v3* 30 days post-SA

[a] ANOVA Fisher *f* test

**Table 4** Number of stapled anopexy patients who had taken at least one 500 mg paracetamol tablet overall at each scheduled visit

| Scheduled visit | Group A | Group B | *P* values |
|---|---|---|---|
| v1 | 27 | 33 | ns[a] |
| v2 | 11 | 25 | <0.05[a] |
| v3 | 1 | 12 | <0.05[a] |

*Group A* patients administered Venoplant for 30 days after stapled anopexy (SA), *Group B* patients administered placebo for 30 days after SA, *v1* 7 days post-SA, *v2* 15 days post-SA, *v3* 30 days post-SA, *ns* not significant ($p > 0.05$)

[a] ANOVA Fisher *f* test

costs. This analysis considers only the cost of drug acquisition (Venoplant®; Aesculapius, Brescia, Italy), expressed in 2016 prices. The average daily dosage was three tablets, and drug treatment lasted 30 days. Drug acquisition costs were taken from national sources (Ministry of Health and Inter-ministerial Committee prices—CIPE). Each tablet costs 0.7 €, giving a total weekly cost of 14.70 €. The overall cost of therapy to the patient was therefore 63 €, as the cost was not reimbursed by the national health system. Although this Venoplant therapy costs 63 €, the present study shows good evidence that using Venoplant after SA not only increases patient safety and comfort but also potentially reduces costs associated with the surgery, as the time taken to resume normal activity/return to work was shorter after treatment with Venoplant.

## Conclusions

The present results indicate that Venoplant was efficacious in the management of postoperative bleeding, especially during the first 2 weeks after surgery; Venoplant was less effective 15–30 days after SA. Venoplant administration also effectively reduced the incidence of TH and reduced postoperative pain compared with placebo. The data provided here can be used to undertake a much larger randomized clinical trial on the effects of Venoplant on the prevention of bleeding, thrombosis, and pain after SA.

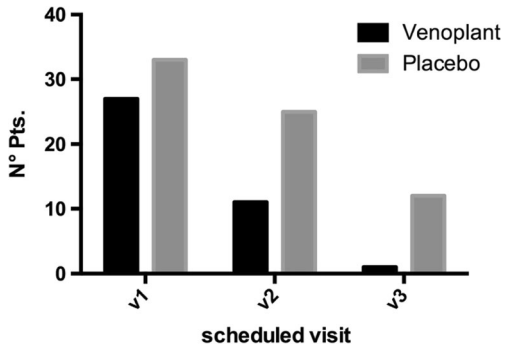


**Fig. 5** Paracetamol assumption

**Acknowledgments** We thank Mr. Simone Teso, MD (University of Padua, Italy), for performing the statistical analyses.

**Compliance with ethical standards**

**Conflict of interest** Aesculapius Pharmaceuticals (Brescia, Italy) provided Venoplant, the placebo, and paracetamol tablets. The authors enrolled patients independently and did not provide access to data or results to staff from Aesculapius Pharmaceuticals. Statistical analyses were undertaken in a blinded fashion by an independent statistician who communicated the results to the authors only at the end of the study.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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