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TachoSil® grafting in tunical lengthening surgery for Peyronie's disease: a single-center experience

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Abstract

Background: In patients with Peyronie's disease with severe/complex penile deformities, a tunical lengthening procedure with grafting is recommended. However, it is unclear which graft is the best. We aim to evaluate the use of TachoSil®, a collagen fleece hemostatic patch, at a single high-volume center. **Methods**: We conducted a retrospective study including all patients who underwent tunical lengthening with TachoSil® at our center until June 2024. Demographic data, personal history, erectile function, characteristics of the curvature and the fibrotic plaque, complications and surgical outcomes were collected. Questionnaires were applied to evaluate patient-reported outcomes and satisfaction. **Results**: A total of 31 patients, 58.38 ± 5.24 years old, underwent the procedure. There was a high postoperative straightness rate and most patients were satisfied with the surgery (73.9%). There was a statistically significant increase in stretched penile length immediately after surgery (p = 0.017), despite a reported decrease in penile length after surgery in 74.2% of the patients. There was a significant decrease in International Index of Erectile Function-5 scores postoperatively (p = 0.001), with a rate of *de novo* erectile dysfunction (ED) of 43.3%, though mild in almost all cases. **Conclusions**: Our findings suggest acceptable results with TachoSil® grafting in terms of patient satisfaction, effective curvature correction and manageable complications. Despite a high incidence of *de novo* ED, most cases were mild and responsive to oral therapy. Complications such as reduced rigidity, glans hypoesthesia and subjective loss of penile length—though largely undocumented objectively—emerged as notable patient concerns.

Keywords

Penile lengthening; Peyronie's disease; TachoSil

Injerto de TachoSil® en la cirugía de alargamiento tunical para la enfermedad de Peyronie: una experiencia en un solo centro

Resumen

Antecedentes: En pacientes con enfermedad de Peyronie con deformidades penianas severas/complejas, se recomienda un injerto de alargamiento tunical. Sin embargo, no está claro cuál injerto es el mejor. Nuestro objetivo es evaluar el uso de TachoSil®, un apósito hemostático de colágeno, en un solo centro de alto volumen. **Métodos**: Realizamos un estudio retrospectivo que incluyó a todos los pacientes que se sometieron a alargamiento tunical con TachoSil® en nuestro centro hasta junio de 2024. Se recopilaron datos demográficos, antecedentes personales, función eréctil, características de la curvatura y la placa fibrosa, complicaciones y resultados quirúrgicos. Se aplicaron cuestionarios para evaluar los resultados informados por los pacientes y la satisfacción. **Resultados**: Un total de 31 pacientes, con una edad promedio de 58.38 ± 5.24 años, se sometieron al procedimiento. Hubo una alta tasa de rectitud postoperatoria y la mayoría de los pacientes estaban satisfechos con la cirugía (73.9%). Hubo un aumento estadísticamente significativo en la longitud del pene estirado inmediatamente después de la cirugía ($p = 0.017$), a pesar de una disminución reportada en la longitud del pene después de la cirugía en el 74.2% de los pacientes. Hubo una disminución significativa en las puntuaciones del Índice Internacional de Función Eréctil-5 postoperatoriamente ($p = 0.001$), con una tasa de disfunción eréctil (DE) *de novo* del 43.3%, aunque leve en la mayoría de los casos. **Conclusiones**: Nuestros hallazgos sugieren resultados aceptables con el injerto de TachoSil® en términos de satisfacción del paciente, corrección efectiva de la curvatura y complicaciones manejables. A pesar de la alta incidencia de DE *de novo*, la mayoría de los casos fueron leves y respondieron a la terapia oral. Complicaciones como la reducción de la rigidez, la hipoestesia del glande y la pérdida subjetiva de longitud del pene—aunque en gran medida no documentadas objetivamente—emergieron como preocupaciones notables para los pacientes.

Palabras Clave

Alargamiento del pene; Enfermedad de Peyronie; TachoSil

1. Introduction

Peyronie's disease (PD) is a condition of the tunica albuginea that affects wound healing and results in the formation of an exuberant scar, which, if severe, may impair sexual intercourse. Although the precise etiology of PD is unknown, it is thought to arise from repeated microvascular injury or trauma to the penis, which in susceptible males triggers an aberrant wound healing response that leads to penile deformity [1, 2]. Contrary to popular belief, PD is not uncommon; its prevalence can be as high as 20% [3], with peak age of onset in the early 50s, and it is a condition associated with significant psychological distress [4, 5].

In men with significant penile deformity, difficulty with intercourse, failed conservative or medical treatment, extensive plaques or patient preference, surgery may be indicated, as long as patients have stable disease for at least three months [6, 7]. There are currently numerous different techniques described to treat PD. In patients without underlying erectile dysfunction (ED) who have severe curvature, complex abnormalities or considerable penile shortening, tunical lengthening [8] using grafts is the recommended course of action [6, 7]. A wide variety of graft materials are available, including autologous grafts (*e.g.*, venous and buccal mucosa grafts), allografts (*e.g.*, cadaveric fascia lata and pericardium), synthetic grafts (*e.g.*, collagen fleece hemostatic patches), and xenografts (*e.g.*, porcine intestinal submucosa and bovine pericardium). While no single graft has been conclusively proven superior, each offers distinct advantages and limitations in terms of biocompatibility, ease of application and impact on surgical outcomes such as erectile function and penile length.

TachoSil® (Baxter, IL, USA), a collagen fleece hemostatic patch, is a xenograft that emerges as a promising surgical graft material, given its excellent biocompatibility, ease of application and additional hemostatic effect [9, 10]. In a recent systematic review and meta-analysis, Natsos A. *et al.* [11] compared the different grafts available. TachoSil®'s studies obtained the second-best postoperative straightness despite having a larger preoperative mean curvature. Unlike xenografts like porcine intestinal submucosa and bovine pericardium, TachoSil® was associated with lower rates of postoperative ED and could even aid penile length preservation, with studies noting an increase of up to 1.1 cm. Its suture-free application reduces operative time, offering an advantage over grafts requiring harvesting or complex handling.

The aim of this study is to evaluate our center experience of tunical lengthening using TachoSil®, describing the functional outcomes, surgical complications and patient-reported satisfaction.

2. Materials and methods

2.1 Study design and participants

Cohort study in which retrospective data were collected for patients with stable PD (absence of pain and no progression of the curvature for at least three months) and severe (curvature of >60°) or complex deformities (*e.g.*, hourglass), without ED or with ED responsive to oral medical therapy, who underwent tunical lengthening procedure using TachoSil® at our institution between June 2017 and June 2024. Patients with penile prosthesis placement were excluded from this study.

2.2 Preoperative evaluation

Before surgery, all patients underwent a comprehensive preoperative evaluation, which included a detailed medical and

sexual history, a physical examination including stretched penile length, and home (self) photography of a natural erection. Penile length was measured by the assistant physician, with the patient positioned supine, and the penis stretched longitudinally by holding the glans without causing discomfort. A measuring tape was placed along the dorsal side of the penis, measuring from the base to the tip of the glans. Penile Duplex Doppler Ultrasonography (PDDU) after intracavernosal administration of 10 to 20 micrograms of commercial Prostaglandin E1 (Caverject®) was performed in selected cases, to exclude vasculogenic ED following our protocal as previously described [12]. Demographic data and data related to personal history were collected. Erectile function was also assessed using the International Index of Erectile Function-5 (IIEF-5) questionnaire. Additionally, patients were informed about the nature of the procedure, its potential risks and its benefits.

2.3 Surgical procedure

All procedures were performed by the same experienced surgeon (AM). Under general anesthesia and after administration of prophylactic antibiotic cefazolin, a subcoronal incision with or without circumcision and complete degloving of the shaft was made. A bilateral incision of Buck's fascia was performed with dissection of the dorsal vascular-nervous bundle of the penis, exposing the tunica albuginea and the fibrotic plaque. Penile curvature was assessed intraoperatively using an artificial saline erection test, and after penile clamping with a rubber band, an I or double-Y incision was made according to the curvature and hourglass effect in order to achieve maximal tunical lenghtening. The defect was then measured and covered using TachoSil® which was applied directly to the tunical defect without suture fixation. An additional graft margin of at least 0.5 cm was used. Finally, Buck's fascia and the skin were closed. In the end, a penile compressive dressing was applied to the shaft and was removed after 2 to 5 days, after which patients were prescribed tadalafil 5 mg daily and were taught postoperative rehabilitation with daily penile manual stretching. Patients were advised to abstain from sexual activity for 4 weeks. Peri-operative complications, tunica albuginea's defect length, width, area and surgery time were recorded. The penile length immediately after tunical incision was also noted.

2.4 Follow-up

Patients were assessed at least 1, 4 weeks, 3 and 12 months post-procedure, and yearly thereafter. During the follow-up, patients were asked to answer some questionnaires: IIEF-5, which classifies patients as having no ED (23–25 points), mild ED (17–21 points), mild to moderate ED (12–16 points), moderate ED (8–11 points) and severe ED (5–7 points) ; a non-validated questionnaire to assess patient-reported long-term surgical outcomes and complications [13] (**Supplementary material 1**); a non-validated modified Erectile Dysfunction Inventory of Treatment Satisfaction [13] (EDITS) in which questions 3–6 and 9–11 were excluded, as they are not useful to evaluate surgical treatment of PD (**Supplementary material 2**), in which a score of 50 or more was considered as the cut-off for satisfaction according to the earlier research conducted by our institution [13] and the study performed by Cappelleri *et al*. [14]; a non-validated Complementary Satisfaction Questionnaire [13] (CSQ) of three questions (**Supplementary material 3**). *De novo* ED was defined as a baseline of >21 plus an IIEF-5 ≤21 after surgery. As this grafting technique does not allow for intraoperative assessment of residual curvature, curvature recurrence was the one subjectively perceived by the patient in the follow-up appointments and reported in the questionnaire. Penile stretched length was measured once more.

An independent review of the data was conducted by two evaluators (MH and AS) to mitigate retrospective biases.

2.5 Statistical analysis

Data were analyzed using SPSS software version 29.0.2.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize baseline characteristics of the population, penile curvature parameters and perioperative data, and functional outcomes after surgery. Results are presented as mean ± standard deviation (SD) or median (interquartile range) for continuous variables, and as absolute numbers (percentages) for categorical variables. Comparison between preoperative and postoperative outcomes was done with paired *t*-test (if data is normally distributed) or Wilcoxon signed-rank test (if not). To analyse the impact of penile curvature parameters and perioperative data on outcomes we used linear regression. To identify predictors of surgical outcomes we used logistical regression. A p-value of < 0.05 was considered statistically significant. All analyses were two-tailed.

3. Results

Between June 2017 and June 2024, 31 consecutive patients with a median age of 59 (27) years underwent tunical lengthening surgery using TachoSil® at our institution. The mean follow-up time was 25.0 ± 20.0 months. Their baseline characteristics are described in Table 1.

The most frequently reported comorbidity was essential hypertension (38.7%). None of them had a history of penile trauma or pelvic surgery. Two of them (6.5%) had previous genital surgery (one underwent a circumcision and the other Nesbit procedure). Of notice, two (6.5%) had mild ED controlled phosphodiesterase type 5 inhibitors (iPDE5). A preoperative PDDU was performed in 38.7% (n = 12) and the median time from diagnosis to surgery was 8 (17) months. Median baseline IIEF-5 was 23 (25) points and the median stretched penile length was 10.0 (6.5) cm.

Concerning the curvature and plaque, the median curvature angle was 90° (45), most commonly on the proximal third and dorsal aspect of the penis; 32.3% (n = 10) had an hourglass deformity. For more detailed data related to the penile curvature parameters and perioperative data, see Table 2.

The functional outcomes of the surgery are depicted in Table 3.

Regarding surgical complications, there were only two mild hematomas and no reported infections. The range of postoperative penile straightness was 93.5%. 43.3% (n = 13) had *de novo* erectile dysfunction, mostly mild, with 29% (n =

TABLE 1. Baseline characteristics of the population (N = 31).

Age (yr) (median, IQR)	59.0 (27)
Comorbidities (%, n)	
Hypertension	38.7 (12)
Dyslipidemia	22.6 (7)
Diabetes	29.0 (9)
Penile trauma	0.0 (0)
Genital surgery	6.5 (2)
Pelvic surgery	0.0 (0)
Erectile dysfunction	6.5 (2)
PDDU (%, n)	38.7 (12)
Baseline IIEF-5 (points) (median, IQR)	23.0 (25)
Baseline IIEF score categories (%, n)	
No ED	100.0 (27)
Mild ED	0.0 (0)
Mild to moderate ED	0.0 (0)
Moderate ED	0.0 (0)
Severe ED	0.0 (0)
Time from beginning of symptoms to appointment (mon) (median, IQR)	12.0 (95)
Time from diagnosis to surgery (mon) (median, IQR)	8.0 (17)
Time from beginning of symptoms to surgery (mon) (median, IQR)	19.0 (97)
Stretched penile length (median, IQR)	10.0 (6.5)

IQR: Interquartile range; PDDU: Penile Duplex Doppler Ultrasonography; IIEF-5: International Index of Erectile Function-5; ED: erectile dysfunction.

TABLE 2. Penile curvature parameters and perioperative data.

Median curvature angle (°) (median, IQR)	90.0 (45)
Mean plaque area (cm^2) (median, IQR)	500.0 (495)
Curvature angulation (%, n)	
Dorsal	67.7 (21)
Lateral left	12.9 (4)
Mixed	19.4 (6)
Curvature location (%, n)	
Proximal third	38.7 (12)
Middle third	35.5 (11)
Distal third	25.8 (8)
Incision type (%, n)	
Double-Y	51.6 (16)
I	48.4 (15)
Hourglass deformity (%, n)	32.3 (10)

IQR: Interquartile range.

TABLE 3. Functional outcomes after surgery.

IIEF-5 (points) (median, IQR)	22.0 (17.0)
Modified EDITS score (median, IQR)	68.8 (87.5)
Satisfied (%, n)	73.9 (17)
De novo erectile dysfuntion (%, n)	43.3 (13)
Mild	30.0 (9)
Mild to moderate	16.7 (5)
Moderate	0.0 (0)
Severe	3.3 (1)
Stretched penile length (median, IQR)	
Immediate	11.8 (5.5)
1-month after surgery	11.5 (6.0)
Patient-reported outcomes (%, n)	
Decreased penile length	74.2 (23)
Diminished rigidity	35.5 (11)
Glans hyposthesia	35.5 (11)
Palpation of surgical knots	9.7 (3)
Curvature recurrence	6.5 (2)
Penile pain	6.5 (2)
Overall satisfaction with sex life (%, n)	
More satisfied	26.1 (9)
Equally satisfied	34.8 (8)
Less satisfied	39.1 (6)
Would you repeat if the same circumstances were posed?	
Yes	70.8 (17)
No	29.2 (7)
Would you recommend it to a friend if the same circumstances were posed?	
Yes	66.7 (16)
No	33.3 (8)

IQR: interquartile range; IIEF-5: International Index of Erectile Function-5; EDITS: Erectile Dysfunction Inventory of Treatment Satisfaction.

9) needing phosphodiesterase type 5 inhibitors (iPDE5) for life and one patient needing placement of a penile prothesis. Postoperative IIEF-5 was 22 (17) points, with a mean decrease of 3.4 ± 3.6 points and the median stretched penile length was 11.75 (5.5) cm, with a mean increase of 0.7 ± 1.1 cm. Based on the modified EDITS, 73.9% (n = 17) are satisfied with the procedure. The most common patient reported complications was decreased penile length (74.2%, n = 23), and diminished rigidity and glans hyposthesia (35.5%, n = 11). Only two (6.5%) referred curvature recurrence. The majority of the patients would repeat (70.8%) and recommend the surgery to a friend (66.7%) if the same circumstances were posed.

When comparing pre- and postoperative outcomes, there's a statistically significant difference between the IIEF-5 scores before and after surgery (p = 0.001) and between stretched penile length before and immediately after surgery (p = 0.017).

Linear regression multivariable analysis did not find a statistically significant impact of time from diagnosis to surgery, surgical time, curvature angle and area of plaque on patient satisfaction as measured by the modified EDITS score (Table 4).

TABLE 4. Impact of surgical parameters on patient satisfaction.

Variable	p-value
Time from diagnosis to surgery	0.095
Surgery time	0.465
Curvature angle	0.197
Plaque area	0.315

Logistical regression multivariable analysis failed to identify predictors of patient satisfaction (Table 5).

TABLE 5. Predictors of patient satisfaction.

Variable	*p*-value
Time from diagnosis to surgery	0.293
Surgery time	0.183
Curvature angle	0.505
Plaque area	0.545
Penile length immediately before surgery	0.208
Penile length 1-month after surgery	0.267
Baseline IIEF	0.296
IIEF after surgery	0.176

IIEF: International Index of Erectile Function.

4. Discussion

The present study evaluates the long-term outcomes of patients with PD submitted to a tunical lengthening procedure using TachoSil®. This research addresses a notable gap, as evidence for this type of graft remains limited, with most studies involving small sample sizes with the exception of one case series [9]. However, its benefits, including reduced operative times, ease of application and proven efficacy, are noteworthy. To our knowledge, only one other study evaluates plaque incision rather than excision grafting with this material [15], underscoring the originality of our findings.

The outcomes reveal a high postoperative straightness rate, with only 6.5% of patients experiencing residual curvature, which in all cases was less than 30°. Moreover, the majority of patients were satisfied with the surgery (73.9%) as indicated by the modified EDITS score, with the majority expressing willingness to repeat (70.8%) the procedure and recommend (66.7%) it to others. Statistically significant improvements were observed in stretched penile length immediately after surgery ($p = 0.017$), but not after one month.

Our findings are consistent with existing literature, in which the range of postoperative straightness is between 83.3% [16] and 100% [17] affirming that TachoSil® achieves high rates of postoperative straightness, even in patients with severe preoperative curvatures [11]. Additionally, the average increase in stretched penile length observed (0.7 ± 1.1 cm) aligns with findings from a recent systematic review [11], reinforcing the consistency of these outcomes across studies.

The procedure demonstrated safety, with few complications reported. However, the relatively low percentage of patients willing to recommend the surgery (66.7%) warrants further exploration. While objective outcomes such as high rates of curvature correction and increased penile length were achieved, subjective dissatisfaction may stem from lingering concerns about postoperative complications, such as a decrease in penile length after surgery in as much as 74.2% of the patients. Besides, 35.5% reported diminished rigidity and the rate of *de novo* ED as objectified by the IIEF-5 score was as high as 43.3%, even though mild in most cases. Accordingly, there was a significant decrease in IIEF-5 scores postoperatively from 23 (17) to 22 (17) ($p = 0.001$).

Glans hyposthesia was also frequently perceived (35.5%). This complication is notable, as it directly impacts patient satisfaction and the perceived success of the procedure. The etiology of glans hypoesthesia is multifactorial and may result from intraoperative manipulation of the neurovascular bundle, postoperative edema or scar formation affecting sensory nerve conduction. Compared to other grafts, the incidence of hypoesthesia observed with TachoSil® appears to fall within a moderate range. For example, studies evaluating porcine small intestinal submucosa grafts reported hypoesthesia in 20–40% of cases, while rates as high as 56.5% have been reported with testicular vaginal tunica grafts [18]. Buccal mucosa grafts (BMG), on the other hand, tend to demonstrate lower rates of sensory changes, likely due to differences in surgical handling and the mechanical properties of the graft itself [11].

Despite the objective increase in penile length after surgery, most patients reported a perceived decrease in penile length. Patients' perceptions of surgical outcomes can be heavily influenced by the preoperative effects of PD, as fibrotic changes and curvature associated often lead to significant penile shortening, which may alter patients' recollections of their original penile state. Consequently, even when objective measures show an increase in penile length postoperatively, patients may perceive no improvement or even a decrease, as their mental benchmark is based on a pre-disease state. Additionally, the psychological distress caused by PD, including anxiety and depression, can amplify negative perceptions. To address this, preoperative counseling is essential to set realistic expectations. Patients should be educated on the irreversible changes caused by PD, the goals of surgery and the likely outcomes. Using objective preoperative measurements, visual aids and tailored communication can help align patient expectations with achievable surgical results, ultimately improving satisfaction.

Regarding erectile function, this study reports a higher rate of *de novo* ED (43.3%) compared to the 0–21% described in the literature [11], which may be explained to the higher degree of penile curvature and prevalence of comorbidities. Almost half the men of our series were older than 60 years old and 29% were diabetic, these two factors are known to increase the risk of post-operative ED and this may have led to the high ED rate. Methodological differences across existing studies also contribute to this variation, as most publications do not consistently define *de novo* ED. While some studies relied on changes in IIEF scores, others used different questionnaires or solely depended on patient-reported outcomes. Moreover, inclusion criteria also varied. For instance, Hatzichristodoulou *et al.* [9] in the study with the largest sample size to date, reported a *de novo* ED rate of 15.7%; however, their cohort included only patients with normal preoperative sexual function. This heterogeneity in assessment criteria makes direct comparison between studies challenging and may contribute to the variability in reported rates. It is worth noting the study by Rico *et al.* [18] which explored the use of testicular vaginal tunica grafts and demonstrated a high success rate of 95.6% in functional stretching with a low incidence of postoperative ED (4.4%). This suggests that autologous grafts may offer certain advantages in minimizing ED and achieving favorable outcomes. Contrary to what our group found for porcine small intestinal submucosa grafting, tunical defect area was not a predictor of *de novo* ED. Importantly, most cases of ED were

mild and controlled with iPDE5, and only one patient required a penile prosthesis, indicating that the procedure remains a viable option for addressing severe deformities while balancing risks to erectile function.

The strengths of this study include its comprehensive design, which incorporates both objective outcomes (*e.g.*, IIEF-5 scores) and subjective patient-reported outcomes, such as the modified EDITS and satisfaction questionnaires, following an a priori protocol. Additionally, the procedure was performed by a single experienced surgeon, ensuring consistency and reducing variability in surgical technique.

Nonetheless, several limitations must be acknowledged. The small sample size of 31 participants reduces the study's power to detect statistically significant relationships in regression analyses, underscoring the need for larger sample sizes in future research. The retrospective nature of data collection is another limitation, as it is prone to selection and recall bias; prospective studies would yield more robust and reliable data. The use of non-validated questionnaires, such as the modified EDITS and other supplementary tools, further limits the comparability and reliability of satisfaction and complication assessments. Moreover, the absence of a control group precludes direct comparisons with other grafting materials or surgical approaches. A prospective study with a control group could significantly improve external validity, offering more robust comparisons between TachoSil® and alternative techniques while minimizing selection and recall bias. This would enable better evaluation of both objective outcomes and patient-reported satisfaction, which are crucial for optimizing surgical management of PD. Larger multicenter studies would provide a more generalizable data set, allowing for more meaningful statistical analyses and identification of predictors of outcomes. Additionally, this grafting technique does not allow for intraoperative measurement of residual curvature, and no objective assessment of erectile function and penile curvature was included in the follow-up, limiting the evaluation of functional outcomes.

5. Conclusions

Our findings suggest acceptable results with TachoSil® grafting in terms of patient satisfaction, effective curvature correction and manageable complications. Despite a high incidence of *de novo* ED, most cases were mild and responsive to oral therapy. Complications such as reduced rigidity, glans hypoesthesia and subjective loss of penile length—though largely undocumented objectively—emerged as notable patient concerns. This study supports the feasibility of TachoSil® grafting in tunical lengthening surgery, with a generally favorable satisfaction rate among patients.

Future research should focus on comparing TachoSil® in larger prospective cohorts to provide a more comprehensive understanding of its efficacy and safety profile, and use validated questionnaires in order to strengthen the reliability of the results and enhance comparability with other studies. Additionally, the importance of preoperative communication with patients cannot be overstated. Surgeons should prioritize addressing subjective concerns, such as the perception of penile length, which remains a frequent source of dissatisfaction. By setting realistic expectations and educating patients on the potential outcomes and limitations of the procedure, the overall satisfaction rates could be further improved.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

AM—contributed to conception and design of the research study and provided help and advice and critically revised the manuscript. MH and ACS—responsible for acquisition; analysis and interpretation of data. MH—wrote the manuscript. PR and CS—provided help and advice and critically revised the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the local ethical committee (approval number: 90/22). Written informed consent was obtained from all participants included in the study in accordance with ethical standards and the Declaration of Helsinki.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://files.intandro.com/files/article/1938976133440520192/attachment/Supplementary%20material.docx.

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