ORIGINAL ARTICLE

Optimizing UV-A Irradiation Profiles in Crosslinking for Keratoconus: Comparison of Outcomes After Standard Accelerated and Topography-Guided Protocols

Otimização de Perfis de Irradiação UV-A no *Crosslinking* em Queratocone: Comparação de Resultados dos Protocolos *Standard* e Topoguiado

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ABSTRACT

INTRODUCTION: Our purpose was to compare visual and tomographic outcomes of crosslinking treatment for progressive keratoconus, utilizing excimer-laser assisted epithelium removal and either central uniform irradiation (C-CXL) or customized, topography-guided irradiation (TG-CXL).

METHODS: Retrospective study. We included patients with progressive keratoconus who underwent TG-CXL or C-CXL. In both procedures the epithelium was removed using phototherapeutic keratectomy (PTK) with a 50 µm ablation within a 7.0 mm optic zone, followed by riboflavin application every 2 minutes for 10 minutes. In TG-CXL this was followed by topography-guided ultraviolet-A (UVA) irradiation, with treatment energies ranging from 5.4 to 10 J/cm2 and fluence of 10 mw/cm^2, while in C-CXL the cornea was uniformly irradiated with UVA with treatment energy of 6.0 J/cm^2 and fluence of 10 mw/cm^2. Patient data was collected at baseline, 6 and 12 months postoperatively including maximum keratometry (Kmax), anterior keratometry values within 5 points of a 3 mm diameter circle centered at the pupil, in the superior and inferior halves of the cornea, central corneal thickness, thinnest point pachymetry, subjective refraction and best corrected visual acuity (BCVA).

RESULTS: Fifty-four eyes from 48 patients were included (27 eyes for each group). Baseline characteristics were not significantly different between groups. Kmax was significantly lower 1 year (-0.83 ± 1.64 D; p=0.016) postoperatively for TG-CXL, but not for C-CXL (-0.46 ± 2.04 D; p=0.256). Inferior-superior (I-S) asymmetry index decreased significantly at 1 year for TG-CXL (-8.17 ± 9.56 D; p<0.001), but not for C-CXL (-3.69 ± 11.69 D; p=0.113). There were no significant differences in the evaluated structural parameters between 6 and 12 months postoperatively in both groups. The BCVA improved significantly at 1 year (difference to baseline: TG-CXL -0.13 ± 0.14 logMAR; p<0.001 and C-CXL -0.24 ± 0.38 logMAR; p=0.018; No difference between groups; p=0.244), while there was a significant myopic increase in spherical refractive error in both groups (difference to baseline: TG-CXL -1.05 ± 2.08 D; p=0.017 and C-CXL -0.90 ± 1.49 D; p=0.025).

CONCLUSION: One year after surgery, TG-CXL leads to greater Kmax reduction and topographic regularization than C-CXL. Both procedures lead to improved visual acuity and a myopic shift, with no superiority among the two. These results support the use of topography-guided crosslinking as a new valuable solution in the treatment of progressive keratoconus.

KEYWORDS: Corneal Topography; Cross-Linking Reagents; Keratoconus; Patient Outcome Assessment; Ultraviolet Rays; Visual Acuity.

RESUMO

INTRODUÇÃO: O objetivo do presente estudo é comparar resultados refrativos e tomográficos do *crosslinking* corneano no queratocone, utilizando laser excimer para remoção do epitélio e irradiação central uniforme (C-CXL) ou irradiação customizada, guiada pela topografia corneana (CXL-TG).

MÉTODOS: Estudo retrospetivo. Foram incluídos pacientes com queratocone em progressão, submetidos a C-CXL ou TG-CXL: Em ambos os procedimentos o epitélio foi removido por queratectomia fototerapêutica, com ablação de 50 μm e zona ótica de 7,0 mm, seguido de aplicação de riboflavina a cada 2 minutos por um período de 10 minutos. No TG-CXL seguiu-se de irradiação topo-guiada com luz ultravioleta A (energias entre 5,4 e 10 J/cm^2, fluência de 10 mw/cm^2), enquanto no C-CXL foi realizada irradiação uniforme com energia de 6,0 J/cm^2 e fluência de 10 mw/cm2. Foram recolhidos dados relativos ao *baseline*, 6 e 12 meses pós-operatório. Os parâmetros avaliados foram a queratometria máxima (Kmax), o valor médio da queratometria anterior em 5 pontos de um círculo centrado na pupila com 3 mm de diâmetro, medidos na metade superior e inferior da córnea, espessura central da córnea, espessura da córnea no ponto mais fino, refração subjetiva e melhor acuidade visual corrigida (MAVC).

RESULTADOS: Foram incluídos 54 olhos de 48 doentes (27 olhos por grupo). As características de *baseline* não eram significativamente diferentes entre grupos. Verificou-se uma redução significativa do Kmax ao 1 ano pós-operatório (-0,83 ± 1,64 D; p=0,016) para o TG-CXL, mas não para o C-CXL (-0,46 ± 2,04 D; p=0,256). O índice de assimetria inferior-superior (I-S) diminuiu significativamente no grupo do TG-CXL (-8,17 ± 9,56 D; p<0,001), ao contrário de no C-CXL (-3,69 ± 11,69 D; p=0,113). Não se verificaram diferenças significativas nos parâmetros estruturais avaliados entre os 6 e 12 meses para ambos os grupos. A MAVC melhorou após 1 ano em ambos os grupos (diferença para o *baseline*: TG-CXL -0,13 ± 0,14 logMAR; p<0,001 e C-CXL -0,24 ± 0,38 logMAR; p=0,018; Sem diferença entre os grupos; p=0,244), havendo também um aumento da miopia para ambos os grupos (diferença para o *baseline*: TG-CXL -1,05 ± 2,08 D; p=0,017 e C-CXL -0,90 ± 1,49 D; p=0,025).

CONCLUSÃO: O TG-CXL leva a uma maior redução do Kmax e regularização topográfica do que o C-CXL. Ambos os procedimentos levam a melhoria da acuidade visual e aumento da miopia, sem superioridade entre estes. Estes resultados apoiam o uso do TG-CXL com um procedimento útil no tratamento do queratocone em progressão.

PALAVRAS-CHAVE: Acuidade Visual; Avaliação do Resultado do Doente; Queratocone; Raios Ultravioleta; Reagentes de Ligações Cruzadas; Topografia da Córnea.

INTRODUCTION

Keratoconus is a bilateral, asymmetric corneal ectasia characterized by progressive corneal thinning and protrusion leading to irregular astigmatism and deterioration of visual acuity.[1,2] Corneal collagen crosslinking (CXL) is an established therapeutic approach with proven effectiveness in halting the progression of keratoconus.[3–5]

The widespread adoption of CXL has fueled multiple lines of research aiming to enhance the original procedure. So far, multiple protocols have been published and are employed globally, expanding on the indications and applications of CXL.[6,7] In conventional CXL, the epithelium is mechanically removed from a central 9 mm zone which is subsequently uniformly irradiated with ultraviolet-A (UVA) light (following riboflavin impregnation).[6] Grentzelos and Kymionis later pioneered the use of transepithelial phototherapeutic keratectomy (t-PTK) as a means for epithelial removal prior to uniform corneal irradiation with UVA, the so-called Cretan protocol. Superior visual, refractive and keratometric outcomes were reported when using this method for epithelium removal.[8,9]

Topography-guided CXL (TG-CXL) is a recent innovation based on the principle that the highest energy should be applied to the most ectatic area for the best outcomes. The reasoning behind this approach is rooted in the belief that in keratoconus, structural weakness is focused on the cone area rather than being uniformly distributed throughout the whole cornea.[10] Therefore, the treatment effect should be aimed at the weak cornea – usually inferiorly – and the superior, stable cornea would need little or no crosslinking. TG-CXL offers surgeons a novel treatment platform that enables personalized corneal irradiation for each corneal phenotype.

Although in TG-CXL most energy will be delivered to the cone, usually the central-inferior cornea, it is not straightforward that the superior cornea is left unchanged by this procedure. The subsequent redistribution of biomechanical stress in the cornea may lead to changes in the superior half of the cornea as well. Thus far, reports have been conflicting, with authors reporting either significant steepening of the superior cornea[11] or no significant changes.[12] However, in studies using manual epithelium removal, there was agreement in regards to a greater flattening of Kmax, and better refractive and visual outcomes of TG-CXL when compared to conventional CXL.[11–13]

This study aims to determine visual and tomographic results within the first year after crosslinking therapy for progressive keratoconus, using t-PTK for epithelial removal and either central uniform irradiation (C-CXL) or tailored, topography-guided irradiation (TG-CXL). We aim to elucidate the distinct impacts of excimer laser epithelial ablation and the UV-A irradiation pattern on corneal regularization.

METHODS

STUDY DESIGN

Retrospective, multicentric study involving two healthcare providers: Department of Ophthalmology, Centro Hospitalar e Universitário de Coimbra (CHUC) and Unidade de Oftalmologia de Coimbra (UOC). The inclusion criteria were patients with progressive keratoconus (progression defined as an increase in maximum keratometry (Kmax) ≥ 1.0 D in the previous year, pachymetry thinning ≥20 μm or 5%, increase in manifest myopia, astigmatism, or spherical equivalent >1.0 D; increase in posterior elevation >15 μm; and decrease of more than 1 Snellen line of corrected distance visual acuity; D-index increase ≥0.42)[14] as measured by corneal tomography [Wavelight Oculyzer II, Alcon Laboratories Inc., Fort Worth, Texas, USA]), that were submitted to TG-CXL or C-CXL. Eyes with previous ocular surgery, concomitant corneal or ocular surface diseases, minimum corneal thickness <325 μm and pregnant or lactating patients were excluded.

SURGICAL PROCEDURE

In both procedures the epithelium was removed using t-PTK (Wavelight Allegretto, Alcon Laboratories Inc., Fort Worth, Texas, USA): a 50 μm ablation within a 7.0 mm optic zone was performed in every patient. Riboflavin 0.1% with hydroxypropyl methylcellulose (HPMC) (VibeX Rapid, Avedro Inc., Waltham, Massachusetts, USA) was then instilled on the cornea every 2 minutes, for a total period of 10 minutes, prior to irradiation.

In TG-CXL this was followed by an individualized UVA irradiation pattern (Mosaic System, Avedro Inc., Waltham, Massachusetts, USA), based on 3 circular/ellipsoid areas centered on the point of thinnest corneal pachymetry. Transitions between zones occurred at the regions of greatest change in anterior axial corneal curvature. The radiance exposure was 10 J/cm^2 in the innermost circle/ellipsoid, 7.2 J/cm^2 in the intermediate and 5.4 J/cm^2 on the outermost circle/ellipsoid (Fig. 1). The fluence was set to 10 mW/cm^2.

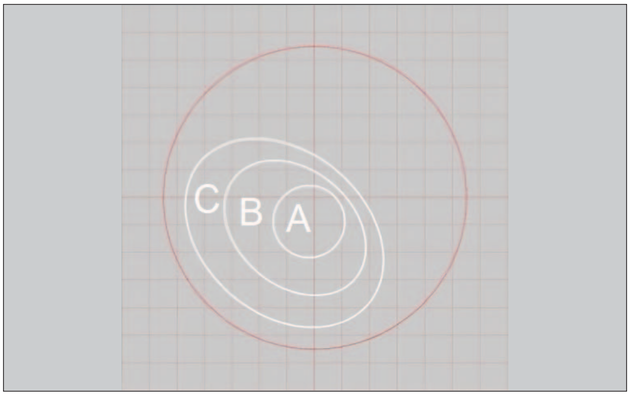

Figure 1. Topography guided crosslinking treatment planification. The radiance exposure is 10 J/cm^2 in the innermost circle (A), 7.2 J/cm^2 in the intermediate ellipsoid (B) and 5.4 J/cm^2 on the outermost ellipsoid (C).

In C-CXL corneal impregnation with riboflavin was followed by uniform corneal irradiation with UVA (KXL System, Avedro Inc., Waltham, Massachusetts, USA). The radiance exposure was 6J/cm^2 and the fluence was set to 10 mW/cm^2.

The postoperative medication regimen for both groups included topical fluoroquinolone drops (moxifloxacin 0.5%, 5 times per day) for one-week, artificial tear drops for one month and an oral non-steroid anti-inflammatory drug (clonixin 300 mg, up to 3 times a day) for 3 days. The operated eye was patched to ease re-epithelialization, after which a topical corticosteroid drop regimen (fluorometholone acetate 0.1%, 4 times per day for a week, followed by a 3-week taper) was started.

DATA COLLECTION

Data was collected from patient's clinical records from baseline, 6 and 12 months postoperatively. Collected variables included best corrected visual acuity (BCVA), subjective refraction sphere and cylinder, Kmax, central corneal thickness (CCT) and pachymetry of the thinnest point. Additionally, the inferior-superior (I-S) asymmetry index was calculated in the following manner: data was collected on the sum of the anterior keratometry values from 5 points in the superior half of the cornea corresponding to the intersection of a 3 mm diameter circle centered at the pupil and the 30º, 60º, 90º, 120º and 150º axes, which was subtracted from the sum of the 5 points corresponding to the intersection of the inferior part of the circle with the 210º, 240º, 270º, 300º, and 330º axes (Fig. 2).

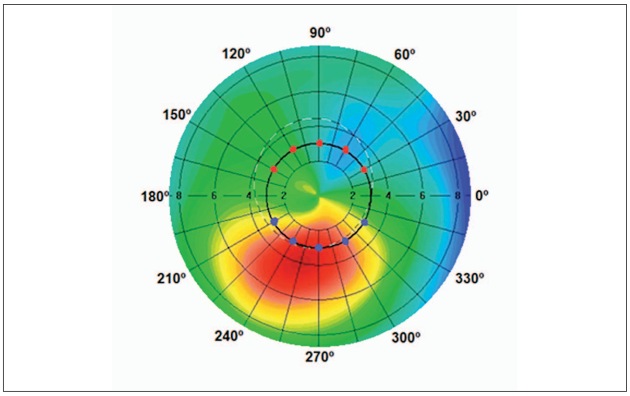

Figure 2. Corneal topography image representing the anterior keratometry values used for the calculation of the Inferior-Superior asymmetry index (I-S index). The sum of the anterior keratometry values on 5 points within a 3 mm ring in the superior half of the cornea (illustrated with red dots) is subtracted from the sum of the anterior keratometry values on 5 points within a 3 mm ring in the inferior half of the cornea (illustrated with blue dots).

STATISTICAL ANALYSIS

Statistical analysis was performed using the software IBM SPSS Statistics version 26.0 (Armonk, New York, USA). Descriptive statistics were computed for all variables. Normality was assessed using the Shapiro-Wilk test. Independent samples t-test was used to compare the two groups on the same dependent variable. Paired samples t-test was used to compare variables at different time points. A p value <0.05 was considered statistically significant.

RESULTS

Fifty-four eyes from 48 patients were included (27 eyes for each group). Most patients were male (61.1%), and the mean age at the time of CXL was 23.6 ± 6.6 years (median of 23 years). Baseline characteristics were not significantly different between both groups (Table 1).

At one year post-operatively, the Kmax and I-S asymmetry index were significantly reduced for the TG-CXL group (-0.83 ± 1.64 D; p=0.016 and -8.17 ± 9.56 D; p<0.001, respectively), but not for C-CXL (-0.46 ± 2.04 D; p=0.256 and -3.69 ± 11.69 D; p=0.113, respectively). Both groups CCT was not significantly changed in this time frame (TG-CXL: -2.2 ± 11.9 µm; p=0.355; C-CXL: -3.8 ± 9.9 µm; p=0.056), but there was a significant reduction in the thinnest pachymetry (TG-CXL: -8.0 ± 12.8 µm; p=0.004. C-CXL: -7.6 ± 16.4 µm; p=0.023). Corneal tomography related outcomes can be found in Table 2.

Table 1. Cohort preoperative characteristics.

	Surgery	Mean ± SD	p-value[A]
Age	TG-CXL	23.6 ± 8.5	1.000
	C-CXL	23.6 ± 4.0	
BCVA (logMAR)	TG-CXL	0.33 ± 0.20	0.439
	C-CXL	0.40 ± 0.37	
Kmax (D)	TG-CXL	56.7 ± 4.2	0.473
	C-CXL	57.7 ± 6.3	
I-S Index	TG-CXL	45.4 ± 17.2	0.453
	C-CXL	49.1 ± 18.7	
CCT (µm)	TG-CXL	473.2 ± 36.9	0.554
	C-CXL	467.0 ± 38.8	
Thinnest Pachymetry (µm)	TG-CXL	446.6 ± 38.5	0.805
	C-CXL	444.1 ± 37.3	

[A] p-value as calculated using an independent samples t-test;

SD – standard deviation; CCT – central corneal thickness.

A typical example for topographic changes following TG-CXL and C-CXL is presented in Fig. 3.

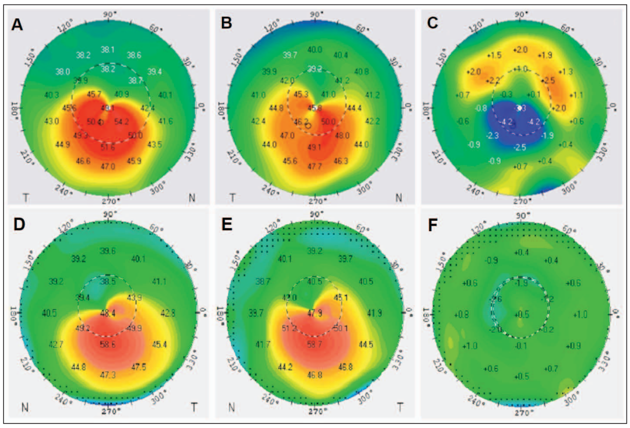

Figure 3. Axial curvature maps of one eye treated with topography guided crosslinking (A-C) and one eye treated with central uniform irradiation crosslinking (D-F). Imaging from baseline (A and D), 12 months after the procedure (B and E) and 12 month-baseline difference map (C and F) is presented.

Manifest refraction and BVCA data were collected for both groups, however, for C-CXL, only 17 out of 27 eyes had complete data on this subject and were used for statistical analysis. Significant improvements in BCVA were registered one year postoperatively for both groups (difference to baseline: TG-CXL -0.13 ± 0.14 logMAR; p<0.001 and C-CXL -0.24 ± 0.38 logMAR; p=0.018), with no significant differences being found in the magnitude of improvement between them (p=0.244). Subjective refraction revealed a significant myopic increase in refraction at the 1-year visit for both groups (sphere change to baseline: TG-CXL -1.05 ± 2.08 D; p=0.017 and C-CXL -0.90 ± 1.49 D; p=0.025).

Table 2. **Corneal tomography changes following topography guided corneal crosslinking (TG-CXL) and central uniform irradiation crosslinking (C-CXL).**

	TG-CXL 1 year (difference to baseline)	C-CXL 1 year (difference to baseline)	TG-CXL 6 – 12 months (difference)	C-CXL 6 – 12 months (difference)
Kmax (D)	-0.83 ± 1.64 ***p*=0.016**	-0.46 ± 2.04 *p*=0.256	+0.16 ± 0.99 *p*=0.457	+0.40 ± 1.44 *p*=0.160
I-S Index (D)	-8.17 ± 9.56 ***p*<0.001**	-3.69 ± 11.69 *p*=0.113	+0.16 ± 4.6 *p*=0.868	+1.47 ± 6.36 *p*=0.239
CCT (μm)	-2.2 ± 11.9 *p*=0.355	-3.8 ± 9.9 p=0.056	+4.3 ± 8.8 ***p*=0.029**	-0.37 ± 8.2 *p*=0.817
Thinnest Pachymetry (μm)	-8.0 ± 12.8 ***p*=0.004**	-7.6 ± 16.4 ***p*=0.023**	+4.0 ± 12.0 *p*=0.128	+1.74 ± 11.4 *p*=0.436

Bold text highlights statistically significant *p* values (<0.05); Kmax – maximum keratometry; I-S – inferior – superior; CCT – central corneal thickness.

DISCUSSION

Previous studies have demonstrated significant improvements in keratometry and visual acuity following TG-CXL for keratoconus.[11–13] These studies however have resorted to mechanical epithelium debridement, which has been linked to inferior results when compared to an excimer-laser assisted epithelium removal approach (in conventional crosslinking).[8,9] Our study aimed to directly compare TG-CXL and C-CXL, both preceded by t-PTK for epithelium removal.

One of the rationales provided by authors to explain the improvement in BCVA after TG-CXL is the regularization of anterior keratometry. Conventional CXL aims for a global strengthening of the stroma by applying the same effect uniformly across the central cornea. This effect is seen in the results of most conventional CXL series: there is uniform central flattening but whatever asymmetry exists before treatment is mostly maintained afterwards.[11,13] With TG-CXL, an asymmetric treatment plan is utilized to obtain an asymmetric flattening effect, one that would globally favor a more regular anterior surface.

In our series, anterior keratometry changes in the superior and inferior halves of the cornea were evaluated using the I-S asymmetry index, corresponding to the difference between the sum of the anterior keratometry values of 5 points within a central 3 mm ring in the inferior and superior corneal halves (Fig. 2). We found a significant change in the I-S index for TG-CXL (*p*<0.001), owing to a mean reduction of 8.17D. This relates to a combination of inferior flattening and superior steepening as was observed by other authors,[11,13] and can be appreciated on an individual basis in the Scheimpflug tomography 12 month-baseline axial curvature difference map (Fig. 3).The same cannot be said for C-CXL as there were no significant changes found in this index (*p*=0.113).

We attribute this TG-CXL associated surface normalization effect to a more advantageous redistribution of biomechanical forces in the stroma. However, one could reasonably argue that the superior corneal steepening might be linked to ongoing progression in the non-crosslinked superior cornea. This could be disputed by our results, which show that the I-S index is unchanged between 6 and 12 months postoperatively (*p*=0.868), with no changes being found for Kmax either in this time frame (Table 2). As such, our data suggests more of an immediate rebalance of the corneal structure, followed by keratometric stability 6 months after the procedure, as is also observed in the C-CXL group (no significant changes for Kmax or I-S index between 6-12 months postoperatively).

Central corneal thickness did not significantly vary at the 1-year time point for either group (TG-CXL: *p*=0.355; C-CXL: *p*=0.817). The thinnest pachymetry was however significantly reduced in both groups at 1 year (mean change of -8.0 μm for TG-CXL, and -7.6 μm for C-CXL). Such a reduction has been previously reported by Seiler, *et al* (2016), although of a greater magnitude (mean change of -18 μm and -17 μm for C-CXL and TG-CXL respectively).[13] Noticeably, Scheimpflug pachymetric measurements following CXL are susceptible to inaccuracies due to haze-induced backscatter,[15] complicating the interpretation of these findings. However, the epithelial ablation using PTK also plays a role, as it was set to 50 μm, and it is known that keratoconus eyes have a thinner epithelial layer in the cone area,[16,17] which means that a small amount of stromal ablation likely takes place.

The BCVA improved significantly at 1 year postoperatively for both groups. Although the improvement in BCVA was on average greater for C-CXL (difference to baseline: TG-CXL -0.13 ± 0.14 logMAR and C-CXL -0.24 ± 0.38 logMAR), there were no significant differences on the magnitude of improvement between both groups (*p*=0.244). Data on refraction and BCVA was not available for all C-CXL eyes (17 out of 27 eyes had complete data across follow-up and were used for statistical analysis), which explains the considerably larger variation in BCVA improvement within the group (standard deviation = 0.38 D). A significant myopic increase in subjective refraction was observed in both groups, which can be partially explained by the used PTK profile, which overcompensates central flattening with a peripheral laser ablation. This has led us to investigate and probably adopt a different profile in the future, although the correction of refractive error is not a main concern for a crosslinking procedure.

Limitations to this study include its retrospective nature and a follow-up limited to one year. Future studies should aim to acquire greater sample sizes and a longer follow-up period.

In conclusion, this study showed that a customized topography-guided crosslinking procedure regularizes the anterior corneal keratometry in keratoconus and leads to a greater reduction in the asymmetry between the superior and inferior cornea and to greater Kmax reduction than C-CXL. This underscores the specific influence of irradiation on corneal regularization in CXL, an effect that can be used in synergy with other established improvements, such as excimer laser-assisted deepithelization. Both procedures lead to improved visual acuity and a myopic shift, with no superiority among the two. These results support the use of topography-guided crosslinking as a new valuable solution in the treatment of progressive keratoconus.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

TC and JG: Responsible for data gathering.and analysis

TC, JG, AR: Responsible for creating the manuscript.

JG, AR, MQJ, JM: Supervised this project and contributed with their expertise to its conclusion.

All authors revised and approved the final manuscript.

TC e JG: Responsáveis pela recolha e análise dos dados

TC, JG, AR: Responsáveis pela redação do manuscrito.

JG, AR, MQJ, JM: Supervisionaram este projeto e contribuíram com os seus conhecimentos para a sua conclusão.

Todos os autores reviram e aprovaram o manuscrito final.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

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