Research Article

Algorithm for Correcting the Keratometric Error in the Estimation of the Corneal Power in Keratoconus Eyes after Accelerated Corneal Collagen Crosslinking

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Purpose. To analyze the errors associated to corneal power calculation using the keratometric approach in keratoconus eyes after accelerated corneal collagen crosslinking (CXL) surgery and to obtain a model for the estimation of an adjusted corneal refractive index ($n_{k_{adj}}$) minimizing such errors. *Methods.* Potential differences (ΔP_c) among keratometric (P_k) and Gaussian corneal power (P_c^{Gauss}) were simulated. Three algorithms based on the use of $n_{k_{adj}}$ for the estimation of an adjusted keratometric corneal power ($P_{k_{adj}}$) were developed. The agreement between $P_{k(1.3375)}$ (keratometric power using the keratometric index of 1.3375), P_c^{Gauss}, and $P_{k adj}$ was evaluated. The validity of the algorithm developed was investigated in 21 keratoconus eyes undergoing accelerated CXL. *Results.* $P_{k(1.3375)}$ overestimated corneal power between 0.3 and 3.2 D in theoretical simulations and between 0.8 and 2.9 D in the clinical study (ΔP_c). Three linear equations were defined for $n_{k_{adj}}$ to be used for different ranges of r_{1c}. In the clinical study, differences between $P_{k_{adj}}$ and P_c^{Gauss} did not exceed ±0.8 D $n_k = 1.3375$. No statistically significant differences were found between $P_{k_{adj}}$ and P_c^{Gauss} ($p > 0.05$) and $P_{k(1.3375)}$ and $P_{k_{adj}}$ ($p < 0.001$). *Conclusions.* The use of the keratometric approach in keratoconus eyes after accelerated CXL can lead to significant clinical errors. These errors can be minimized with an adjusted keratometric approach.

1. Introduction

Our research group has recently published a series of articles reporting the differences obtained theoretically and clinically between the central corneal power estimated using the classical keratometric approach (keratometric corneal power, P_k) and that obtained using the Gaussian equation that considers the curvature of both corneal surfaces and corneal thickness (Gaussian corneal power, P_c^{Gauss}) in healthy [1, 2] and postmyopic LASIK corneas [3]. In the healthy cornea, $P_{k(1.3375)}$ can theoretically overestimate the corneal power (considering P_c^{Gauss} as the reference) up to 2.50 D and in post-LASIK eyes up to 3.50 D if a keratometric corneal refractive index (n_k) of 1.3375 is used. A variable keratometric corneal refractive index depending on r_{1c} (adjusted keratometric index, $n_{k_{adj}}$) was

proposed and clinically validated by our research group as an approach to minimize the error associated to the keratometric estimation of corneal power in healthy and post-LASIK eyes [1–3].

In keratoconus eyes, theoretical and clinical errors associated to the calculation of central corneal power considering P_k have been also analyzed and compared with P_c^{Gauss} [4]. In theoretical simulations, an overestimation of $P_{k(1.3375)}$ was observed in most of cases, with differences among Gaussian and keratometric calculations ($\Delta P_c = P_{k(1.3375)} - P_c^{Gauss}$) ranging from −0.1 to 4.3 D, depending on the r_{1c}/r_{2c} combination and the theoretical eye model considered. Clinically, $P_{k(1.3375)}$ was found to overestimate corneal power in a range between 0.5 and 2.5 D, with a mean clinical difference (ΔP_c) of 1.48 D [4, 5]. The clinical value of the keratometric corneal refractive index matching P_k and $P_c^{Gauss}(n_{k_{exact}})$ ranged from 1.3225 to 1.3314 in a keratoconus population evaluated in a previous study [4]. Eight linear algorithms were developed to estimate the most adequate adjusted corneal refractive index ($n_{k_{adj}}$) minimizing the error associated to the corneal power calculation using the keratometric approach in keratoconus. The value of $n_{k_{adj}}$ ranged from 1.3190 to 1.3324, and from 1.3207 to 1.3339 using the Gullstrand and Le Grand eye models, respectively. Using this $n_{k_{adj}}$ for corneal power calculation, differences between $P_{k_{adj}}$ and P_c^{Gauss} were found to be clinically in the range within ±0.70 D. The aim of the current study was to analyze theoretically and clinically the errors associated to corneal power calculation using the keratometric approach in keratoconus eyes after accelerated corneal collagen crosslinking surgery and to obtain a model for the estimation of an adjusted corneal refractive index ($n_{k_{adj}}$) minimizing such errors.

2. Methods

2.1. Theoretical Calculations. Central corneal power was calculated using the classical keratometric corneal refractive index (1) and also using the Gaussian equation (2) that considers the contribution of both corneal surfaces and corneal thickness. Differences among both types of central corneal power calculations were determined (4 and 6) and modelled by regression analysis. All calculations and simulations were performed using the Matlab software (Math Works Inc., Natick, MA, USA).

2.2. Calculation of the Gaussian and Keratometric Corneal Power. The keratometric power (P_k) was estimated by means of the following expression:

$$P_k = \frac{n_k - 1}{r_{1c}}, \tag{1}$$

where n_k is the keratometric corneal refractive index and r_{1c} is the radius of the anterior corneal surface.

The Gaussian corneal power was calculated by using the formula based on Gaussian optics in paraxial approximation:

$$P_c^{Gauss} = P_{1c} + P_{2c} - \delta P_{1c} P_{2c}$$
$$= \frac{n_c - n_a}{r_{1c}} + \frac{n_{ha} - n_c}{r_{2c}} - \frac{e_c}{n_c} \frac{n_c - n_a}{n_c} \frac{n_{ha} - n_c}{r_{2c}}, \tag{2}$$

where P_c^{Gauss} is the total Gaussian corneal power, P_{1c} is the anterior corneal power, P_{2c} is the posterior corneal power, r_{1c} is the anterior corneal radius, r_{2c} the posterior corneal radius, n_a the refractive index of air, n_c the refractive index of the cornea, n_{ha} the refractive index of the aqueous humor, and e_c is the central corneal thickness.

2.3. Calculation of the Adjusted Corneal Refractive Index. As in our previous studies [1–3, 5], the adjusted corneal refractive index ($n_{k_{adj}}$) was defined as the value associated to an equivalent difference in the magnitude of ΔP_c for the extreme values of r_{2c} corresponding to each r_{1c} value and eye model. Specifically, for each r_{1c} value considered, $n_{k_{adj}}$ was obtained with the following equation: $\Delta P_c(r_{2c_{min}}) = \Delta P_c(r_{2c_{max}})$. The adjusted keratometric corneal power ($P_{k_{adj}}$) can be calculated using the classical keratometric corneal power formula as follows:

$$P_{k_{adj}} = \frac{n_{k_{adj}} - 1}{r_{1c}}. \tag{3}$$

2.4. Differences among Gaussian and Keratometric Approaches. By using (1) and (2), the differences between the keratometric and the Gaussian corneal power (ΔP_c) were calculated with the following expression:

$$\Delta P_c = P_k - P_c^{Gauss}$$
$$= \frac{n_k - 1}{r_{1c}} - \left(\frac{n_c - n_a}{r_{1c}} + \frac{n_{ha} - n_c}{r_{2c}} - \frac{e_c}{n_c} \cdot \frac{n_c - n_a}{r_{1c}} \cdot \frac{n_{ha} - n_c}{r_{2c}} \right). \tag{4}$$

Expression (4) was simplified by including the concept of k ratio (5) as follows:

$$k = \frac{r_{1c}}{r_{2c}}, \tag{5}$$

$$\Delta P_c = P_k - P_c^{Gauss}$$
$$= \frac{n_k - 1}{r_{1c}} - \left(\frac{n_c - n_a}{r_{1c}} + \frac{n_{ha} - n_c}{((r_{1c})/k)} - \frac{e_c}{n_c} \cdot \frac{n_c - n_{ha}}{r_{1c}} \cdot \frac{n_{ha} - n_c}{((r_{1c})/k)} \right). \tag{6}$$

2.5. Calculation of the Exact Keratometric Corneal Refractive Index. The calculation of the exact keratometric corneal refractive index ($n_{k_{exact}}$) was performed by making (4) or (6) equal to zero. Considering this, the following expressions were obtained:

$$n_{k_{exact}} = \frac{-e_c n_c + e_c n_c^2 + e_c n_{ha} - e_c n_c n_{ha} - n_c^2 r_{1c} + n_c^2 r_{2c} + n_c n_{ha} r_{1c}}{n_c r_{2c}} \tag{7}$$

or

$$n_{k_{exact}} = \frac{-e_c k n_c + e_c k n_c^2 + e_c k n_{ha} - e_c k n_c n_{ha} + n_c^2 r_{1c} - k n_c^2 r_{1c} + k n_c n_{ha} r_{1c}}{n_c r_{1c}}. \tag{8}$$

2.6. Determination of the Range of Corneal Curvature in Keratoconus Eyes after Corneal Collagen Crosslinking. For our simulations, the range of potential variation of the anterior and posterior corneal curvature in keratoconus after collagen crosslinking surgery (CXL) was defined considering the information reported in previous studies evaluating the outcomes of CXL [6–10]. The definition of the potential values of r_{2c} after CXL that could be used in our theoretical simulations was defined according to previous studies reporting changes occurring in such parameter measured using the Scheimpflug imaging technology [11–13]. According to all previous studies revised, the anterior corneal radius (r_{1c}) was found to range in keratoconus after CXL between 5.6 and 8.5 mm, and the posterior corneal radius (r_{2c}) between 4.4 and 7.0 mm [6–10]. Accordingly, k ratio was found to range between 1.04 and 1.57.

3. Clinical Study

3.1. Patients and Examination. The prospective study includes a total of 21 eyes of 14 patients aged between 23 and 69 years. All patients belonged to the Corneal and Anterior Segment Unit of the Ophthalmology Department (OFTALMAR) of the Vithas Internacional Medimar Hospital (Alicante, Spain). The study inclusion criterion was the presence of progressive keratoconus: central topographic steepening of more than 1 D with refractive change of more than 0.50 D in the last 6 months. The standard criterion for diagnosing keratoconus was used: corneal topography revealing an asymmetric bowtie pattern with or without skewed axes and at least one keratoconus sign on slit-lamp examination, such as stromal thinning, conical protrusion of the cornea at the apex, Fleischer ring, Vogt striae, or anterior stromal scar [14]. Although it is known that keratoconus progression arrests in the 3rd or 4th decade of life, we detected and included some cases in which progression of the disease was detected in patients older than 40 years old. It should be considered that although uncommon, progression of the disease in patients in the 5th decade of life has been reported in some specific cases [15]. The exclusion criteria were previous eye surgery and the presence of any type of active eye disease. All patients were properly informed about their inclusion and signed an informed consent form. The study complied with the principles of the Declaration of Helsinki and was approved by the hospital ethics committee.

A complete ophthalmological examination was carried out preoperatively, which included measurement of manifest refraction, uncorrected (UDVA) and corrected distance visual acuity (CDVA), Goldmann applanation tonometry, anterior segment slit-lamp examination, corneal topography and aberrometry with the Sirius system (Costruzioni Strumenti Oftalmici, CSO, Florence, Italy), biometry (IOL Master v.4.3, Carl Zeiss Meditec, Jena, Germany), and eye fundus examination. Postoperatively, patients were reviewed at 1 day and 1 month after surgery.

3.2. Surgery. All operations were performed by the same expert surgeon (AA) under topical anaesthesia, using the Avedro KXL cross-linking system (Waltham, MA, United States). After separating the eyelids with a blepharostat and applying the anaesthesia, the procedure began with the instillation, every 90 seconds for a total of 4 minutes, of dextran-free hypoosmolar riboflavin drops containing agents to improve the epithelial permeability, including benzalkonium chloride (Paracel, Avedro, Waltham, MA, United States). A benzalkonium chloride-free 0.25% riboflavin solution (VibeX Xtra, Avedro, Waltham, MA, United States) was then instilled at the same rate for 6 minutes. Once these steps had been completed, ultraviolet radiation was applied for 2 minutes and 40 seconds, using a pulsed light protocol (2 seconds on/1 second off). The total energy irradiated was 7.2 J/cm², and the ultraviolet power was 45 mW/cm². After irradiation, the cornea was rinsed with balanced saline solution. As postoperative treatment, the patient was instructed to apply one drop of antibiotic (Tobrex, Alcon Laboratories, Forth Worth, TX, United States) and epithelializing ointment (Oculos Epitelizante, Thea Laboratories, Clermont-Ferrand, France) every 8 hours and to use artificial tears.

3.3. Statistical Analysis. Statistical analysis was performed using the software SPSS version 19.0 for Windows (SPSS, Chicago, IL, USA). Normality of all data distributions was first confirmed by means of the Kolmogorov-Smirnov test. Specifically, the unpaired Student t-test and Wilcoxon test were used for comparing the two approaches for P_c calculation in the theoretical study, keratometric and Gaussian. The Bland-Altman analysis [16] was used for evaluating the agreement and interchangeability of the methods used clinically for obtaining the corneal power (P_k, $P_{k_{adj}}$, and P_c^{Gauss}). Pearson correlation coefficient was used to assess the correlation between ΔP_c and other clinical parameters analyzed. The same level of statistical significance (p value < 0.05) was considered in all analyses.

4. Results

4.1. Theoretical Study

4.1.1. Exact ($n_{k_{exact}}$) and Adjusted Keratometric Corneal Refractive Index ($n_{k_{adj}}$). The value of $n_{k_{exact}}$ considering all possible combinations of r_{1c} (5.6 to 8.5 mm) and r_{2c} (4.4 to 7.0 mm) ranged from 1.3140 to 1.3351 for the Gullstrand eye model (Table 1) and from 1.3157 to 1.3366 for the Le Grand eye model (Table 2).

The value of $n_{k_{adj}}$ ranged from 1.3210 to 1.3309 and from 1.3227 to 1.3325 for the Gullstrand and Le Grand eye models, respectively (Tables 1 and 2). All $n_{k_{adj}}$ values adjusted perfectly to 3 linear equations ($R^2 = 1$) for each model, and therefore 3 theoretical algorithms only depending on r_{1c} were obtained for the calculation of corneal power (Tables 1 and 2).

4.1.2. Differences between P_k and P_c^{Gauss}. If the Gullstrand eye model was used ($n_k = 1.3315$), ΔP_c ranged from an underestimation of −0.7 D ($r_{1c} = 5.6/r_{2c} = 5.4$ mm) to an overestimation of 2.4 D ($r_{1c} = 6.8/r_{2c} = 4.4$ mm). If the Le Grand eye model was used ($n_k = 1.3304$), ΔP_c ranged from −1.2 D to 2.0 D for the same r_{1c} and r_{2c} values. When the value

TABLE 1: Algorithms for $n_{k_{exact}}$ and $n_{k_{adj}}$ developed using the Gullstrand eye model for different r_{1c} and/or k intervals. Likewise, the corresponding theoretical ranges for $n_{k_{adj}}$, $P_{k_{adj}}$, and P_c^{Gauss} and differences (ΔP_c) between $P_{k_{adj}}$ and P_c^{Gauss} are also shown. Minimum and maximum $n_{k_{adj}}$, $P_{k_{adj}}$, and P_c^{Gauss} values are bolded in the table.

r_{1c} (mm)	$[k_{min}, k_{max}]$	$n_{k_{adj}}$ algorithm	$n_{k_{adj}}$	$n_{k_{exact}}$	P_c^{Gauss} (D)	$P_{k_{adj}}$ (D)	ΔP_c (D)
[5.6, 6.8]	[1.04, 1.55]	$-0.00825\, r_{1c} + 1.3771$	**[1.3210, 1.3309]**	[1.3154, 1.3355]	[46.4, **59.9**]	[47.2, **59.1**]	[−0.8, 0.8]
[6.9, 7.2]	[1.15, 1.50]	$-0.00750\, r_{1c} + 1.3770$	[1.3230, 1.3253]	[1.3171, 1.3309]	[44.0, 48.0]	[44.9, 47.1]	[−0.8, 0.8]
[7.3, 8.5]	[1.04, 1.57]	$-0.00656\, r_{1c} + 1.3769$	[1.3211, 1.3290]	[**1.3140**, 1.3351]	[**36.9**, 45.9]	[**37.8**, 45.1]	[−0.8, 0.8]

TABLE 2: Algorithms for $n_{k_{exact}}$ and $n_{k_{adj}}$ developed using the Le Grand eye model for different r_{1c} and/or k intervals. Likewise, the corresponding theoretical ranges for $n_{k_{adj}}$, $P_{k_{adj}}$, and P_c^{Gauss} and differences (ΔP_c) between $P_{k_{adj}}$ and P_c^{Gauss} are also shown. Minimum and maximum $n_{k_{adj}}$, $P_{k_{adj}}$, and P_c^{Gauss} values are bolded in the table.

r_{1c} (mm)	$[k_{min}, k_{max}]$	$n_{k_{adj}}$ algorithm	$n_{k_{adj}}$	$n_{k_{exact}}$	P_c^{Gauss} (D)	$P_{k_{adj}}$ (D)	ΔP_c (D)
[5.6, 6.8]	[1.04, 1.55]	$-0.00819\, r_{1c} + 1.3783$	**[1.3227, 1.3325]**	[1.3171, 1.3370]	[46.6, **58.6**]	[47.4, **59.4**]	[−0.8, 0.8]
[6.9, 7.2]	[1.15, 1.50]	$-0.00744\, r_{1c} + 1.3781$	[1.3245, 1.3267]	[1.3188, 1.3324]	[44.3, 48.2]	[45.1, 47.4]	[−0.8, 0.8]
[7.3, 8.5]	[1.04, 1.57]	$-0.00651\, r_{1c} + 1.3781$	[**1.3227**, 1.3305]	[**1.3157**, 1.3366]	[**37.1**, 46.1]	[**38.0**, 45.3]	[−0.8, 0.8]

of $n_k = 1.3375$ was used, an overestimation was always found, with ΔP_c ranging from 0.3 D ($r_{1c} = 7.3/r_{2c} = 7.0$ mm) to 3.2 D ($r_{1c} = 6.7$ or $6.8/r_{2c} = 4.4$ mm) for the Gullstrand model and from 0.1 D ($r_{1c} = 5.6/r_{2c} = 5.4$ mm or $r_{1c} = 7.3/r_{2c} = 7.0$ mm) to an overestimation of 3.0 D ($r_{1c} = 6.8$ or $r_{2c} = 4.4$ mm) for the Le Grand eye model.

4.1.3. Differences between $P_{k_{adj}}$ and P_c^{Gauss}. $P_{k_{adj}}$ ranged from 37.8 D to 59.1 D, whereas P_c^{Gauss} ranged from 36.9 to 59.9 D for the Gullstrand eye model (Table 1). With the Le Grand eye model (Table 2), $P_{k_{adj}}$ was found to range between 38.0 and 59.4 D and P_c^{Gauss} between 37.1 and 58.6 D. As shown in Tables 1 and 2, differences between $P_{k_{adj}}$ and $P_c^{Gauss} (\Delta P_c)$ did not exceed the value of ±0.8 D.

4.2. Clinical Study. The clinical study comprised 21 eyes of 14 patients with keratoconus, 2 women (14%) and 12 men (86%), with a mean age of 41 ± 17 years (range, 23 to 61 years). The sample comprised 12 (57%) and 9 (43%) left and right eyes, respectively. Main clinical features of the sample evaluated are summarized in Table 3.

4.2.1. Exact ($n_{k_{exact}}$) and Adjusted Keratometric Corneal Refractive Index ($n_{k_{adj}}$). The results for $n_{k_{exact}}$ and $n_{k_{adj}}$ considering the different combinations of r_{1c} and r_{2c} or k values (1.14 to 1.47) are shown in Table 4. The value of $n_{k_{exact}}$ ranged from 1.3182 to 1.3312, and the value of $n_{k_{adj}}$ ranged from 1.3210 to 1.3306. All these values were also within the range obtained in our previous theoretical simulations (see Table 1).

4.2.2. Agreement of $P_{k(1.3375)}$ with P_c^{Gauss}. An overestimation was always present when $P_{k(1.3375)}$ was compared with P_c^{Gauss} that ranged between 0.8 and 2.9 D. Statistically significant differences were found between $P_{k(1.3375)}$ and P_c^{Gauss} (Wilcoxon test, $p < 0.001$). A very strong and

TABLE 3: Mean ocular features of the clinical sample evaluated in the current study.

Parameter	Mean (SD)	Range
r_{1c} (mm)	7.1 (0.60)	5.6 to 7.8
r_{2c} (mm)	5.6 (0.70)	4.4 to 6.6
k	1.2679 (0.09)	1.1404 to 1.4719
Asphericity anterior surface	−0.7 (0.53)	−1.6 to 0.3
Asphericity posterior surface	−0.8 (0.73)	−2.0 to 0.7
$P_{k(1.3375)}$ (D)	48.2 (4.5)	43.3 to 59.9
$P_{k_{adj}}$ (D)	46.6 (4.4)	41.7 to 58.7
P_c^{Gauss} (D)	46.5 (4.1)	42.1 to 57.9
$e_{c_{min}}$ (μm)	452 (47.2)	384 to 546
$e_{c_{central}}$ (μm)	488 (64.6)	418 to 639

statistically significant correlation was found between $P_{k(1.3375)}$ and P_c^{Gauss} ($r = 0.99$, $p < 0.001$). The Bland-Altman analysis showed a mean difference between $P_{k(1.3375)}$ and P_c^{Gauss} of 1.63 D, with limits of agreement of 0.44 D and 2.82 D (Table 5).

A very strong statistically significant correlation was found between clinical $\Delta P_c (P_{k(1.3375)} - P_c^{Gauss})$ and r_{2c} ($r = -0.95$, $p < 0.001$). The correlation of this ΔP_c with r_{1c}, anterior corneal asphericity, and posterior corneal asphericity was moderate ($r_{1c} = -0.77$, $p < 0.001$; QCA $= -0.76$, $p < 0.001$; and QCP $= -0.81$, $p < 0.001$), whereas the correlation was weak with the remaining clinical variables evaluated.

4.2.3. Agreement of $P_{k_{adj}}$ with P_c^{Gauss}. No statistically significant differences were found between $P_{k_{adj}}$ and P_c^{Gauss} ($p > 0.05$), with a very strong and statistically significant correlation between them ($r = 0.98$, $p < 0.01$). A linear

TABLE 4: Values of $n_{k_{exact}}$ and $n_{k_{adj}}$ for different intervals of r_{1c} and the difference between them in terms of corneal power (ΔP_c) in the sample of keratoconus eyes undergoing corneal collagen crosslinking evaluated. Minimum and maximum $n_{k_{exact}}$ and $n_{k_{adj}}$ values are bolded in the table.

r_{1c} (mm)	Number of patients	$[k_{min}, k_{max}]$	$n_{k_{exact}}$	$n_{k_{adj}}$	ΔP_c (D)
[5.6, 6.8]	6	[1.26, **1.47**]	[**1.3182**, 1.3264]	[**1.3210**, **1.3306**]	[0.0, 0.8]
[6.9, 7.2]	5	[1.20, 1.25]	[1.3261, 1.3287]	[1.3228, 1.3294]	[−0.8, 0.1]
[7.3, 8.5]	10	[**1.14**, 1.30]	[1.3254, **1.3312**]	[1.3257, 1.3289]	[−0.5, 0.4]

TABLE 5: Bland-Altman analysis outcomes of the comparison between different methods of corneal power calculation.

	$\Delta P_c \pm SD$ (D)	LoA (D)	p value
$P_{k(1.3375)} - P_c^{Gauss}$	1.63 ± 0.6	0.44 to 2.82	0.000
$P_{k(1.3375)} - P_{k_{adj}}$	1.59 ± 0.4	0.79 to 2.38	0.000
$P_{k_{adj}} - P_c^{Gauss}$	0.09 ± 0.5	−0.98 to 1.16	0.794

dependence was also found between $P_{k_{adj}}$ and P_c^{Gauss} ($P_{k_{adj}} = -2.99 + 1.07 \times P_c^{Gauss}$, $R^2 = 0.99$) (Figure 1). According to the Bland and Altman analysis, the range of agreement between $P_{k_{adj}}$ and P_c^{Gauss} was 0.09 D, with limits of agreement of −0.98 D and 1.16 D (Figure 2 and Table 5). A moderate correlation of the difference between $P_{k_{adj}}$ and P_c^{Gauss} (ΔP_c) with r_{2c} ($r = -0.66$, $p < 0.01$) and the asphericity of the posterior corneal surface was found ($r = -0.70$, $p < 0.01$).

4.2.4. Agreement of $P_{k(1.3375)}$ with $P_{k_{adj}}$. Statistically significant differences were found between $P_{k(1.3375)}$ and $P_{k_{adj}}$ ($p < 0.001$), with a very strong and statistically significant correlation of such variables ($r = 0.98$, $p < 0.001$) (Figure 3). The Bland-Altman analysis showed a mean difference value between $P_{k(1.3375)}$ and $P_{k_{adj}}$ of 1.59 D, with limits of agreement of 0.79 D and 2.38 D (Figure 4 and Table 5). The value of ΔP_c between $P_{k(1.3375)}$ and $P_{k_{adj}}$ correlated significantly with r_{2c} ($r = 0.44$, $p < 0.001$), r_{1c} ($r = -0.39$, $p < 0.001$), and the asphericity of the anterior corneal surface ($r = -0.43$, $p < 0.001$).

5. Discussion

Significant differences in corneal power between the keratometric and Gaussian estimations have been observed in our simulation study using the Gullstrand and Le Grand eye models in keratoconus corneas undergoing CXL, which is consistent with the results of previous studies [1–5]. Specifically, the keratometric estimation has been shown to be able to overestimate or underestimate the corneal power depending on r_{1c}, n_k, or the eye model used in normal healthy [1, 2], post-LASIK [3], and keratoconus corneas [4, 5]. In our simulation study, when $n_k = 1.3375$ was used, $P_{k(1.3375)}$ overestimated P_c^{Gauss} between +0.30 D and +3.2 D and between +0.1 D and +3.0 D for Gullstrand and Le Grand
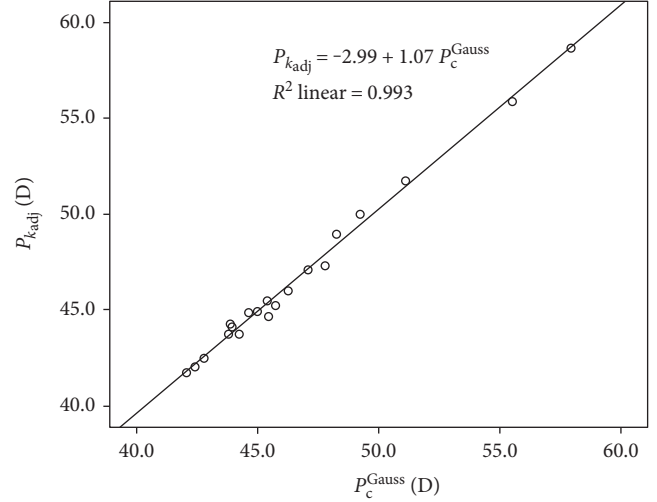

FIGURE 1: Scatterplot showing the relationship among adjusted keratometric ($P_{k_{adj}}$) and Gaussian (P_c^{Gauss}) corneal power. The adjusting line to the data obtained by means of the least-squares fit is shown.

eye models, respectively. A similar outcome was reported in simulations in nontreated keratoconus corneas, although the maximum potential overestimations were higher (ΔP_c ranging from −0.08 D to +4.77 D for Gullstrand eye model and from −0.26 D to +3.97 D for Le Grand eye model) [4]. In contrast, the overestimations have been demonstrated to be lower when the classical keratometric approach is used in normal healthy eyes, with maximal potential overestimations of 2.50 and 2.30 D for the Gullstrand and Le Grand eye models, respectively [1]. Likewise, maximal overestimations of 3.55 D and 3.39 D for Gullstrand and Le Grand eye models, respectively, have been obtained in post-LASIK corneas [3]. Therefore, the keratometric approach is an inaccurate procedure to estimate the corneal power, especially in those cases in which the relationship between the anterior and posterior corneal curvature is altered, such as occurrences after laser refractive surgery [3] and in corneal ectatic diseases [17].

The data obtained in our simulations were found to be consistent with those obtained in the clinical study also conducted in the current research. We evaluated a sample of keratoconus corneas undergoing CXL surgery and found that ΔP_c ranged between +0.8 and +2.9 D when $P_{k(1.3375)}$ and P_c^{Gauss} were compared. Mean difference between corneal
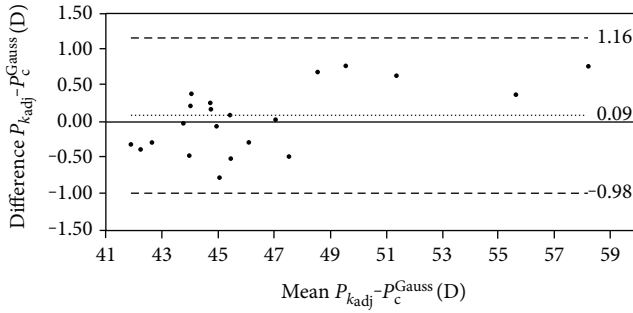
FIGURE 2: Bland-Altman plot showing the differences between the adjusted keratometric $(P_{k_{adj}})$ and Gaussian (P_c^{Gauss}) corneal powers against the mean value of both. The upper and lower lines represent the limits of agreement calculated as mean of differences ±1.96 SD.
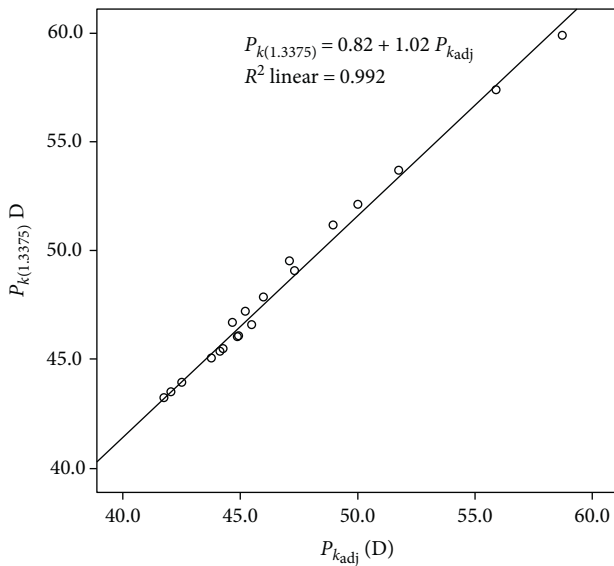

FIGURE 3: Scatterplot showing the relationship among adjusted keratometric $(P_{k_{adj}})$ and classical keratometric $(P_{k(1.3375)})$ corneal power. The adjusting line to the data obtained by means of the least-squares fit is shown.

power estimations was +1.6 D, and this difference was statistically significant. A similar outcome was obtained in a previous study evaluating the keratometric error in nontreated keratoconus, with overestimations between +0.7 and +2.4 D and a mean difference between keratometric and Gaussian corneal powers of +1.4 D [5]. Therefore, a small trend to more overestimation of the keratometric approach is observed in keratoconus once a CXL treatment is applied. An explanation for this fact may be the changes occurring with surgery at the posterior corneal surface leading to altered values of the k ratio [18]. This overestimation must be considered in clinical practice when the changes in corneal curvature after CXL are analysed in order to avoid overestimating the effect of the surgery.

The corneal refractive index avoiding the error when the keratometric approach is used $(n_{k_{exact}})$ was calculated
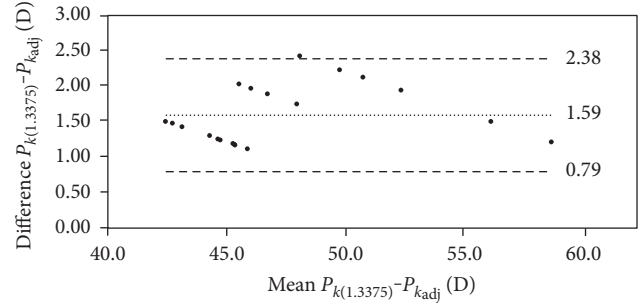

FIGURE 4: Bland-Altman plot showing the differences between the adjusted keratometric $(P_{k_{adj}})$ and classical keratometric $(P_{k(1.3375)})$ corneal powers against the mean value of both. The upper and lower lines represent the limits of agreement calculated as mean of differences ±1.96 SD.

for each r_{1c}-r_{2c} combination in our keratoconus sample with previous CXL. The value of $n_{k_{exact}}$ ranged from 1.3140 to 1.3351 for the Gullstrand eye model and from 1.3157 to 1.3366 for Le Grand eye model in our simulations. Clinically, the value of $n_{k_{exact}}$ ranged from 1.3182 to 1.3312 using the Gullstrand eye model for calculations. This interval is wider than that obtained in nontreated keratoconus eyes, with values ranging from 1.3225 to 1.3314 [5]. This confirms that the variation of k ratio in CXL-treated keratoconus eyes is higher due to posterior corneal surface and volumetric changes. Further studies are needed to confirm the real effect on corneal volume of accelerated CXL. As in previous studies evaluating different ocular conditions, the use of the classical keratometric corneal refractive index $n_k = 1.3375$ was found to be a wrong approach [1, 2, 4, 5].

As devices measuring the curvature of the posterior corneal surface are not available in all clinical settings, an adjusted keratometric approach was developed to calculate the corneal power using the keratometric approximation but with a minimal error associated. We could not use a previous adjusted keratometric algorithm defined by our research group for keratoconus as the variation required for the adjusted corneal refractive index was higher [5]. Consequently, new algorithms were developed using the Gullstrand and Le Grand eye models to obtain the adjusted corneal refractive index $(n_{k_{adj}})$ minimizing the error associated to the keratometric corneal power calculation. Specifically, three different algorithms were defined for different ranges of r_{1c}. With them, $n_{k_{adj}}$ was found to range from 1.3210 to 1.3309 for the Gullstrand eye model and from 1.3227 to 1.3325 for the Le Grand eye model. When $P_{k_{adj}}$ was compared with P_c^{Gauss} in our theoretical simulations, the differences between both corneal power values did not exceed 0.8 D. This difference of 0.8 D was only observed for the maximum and minimum values of r_{2c}.

Once the algorithm is developed, we validated it clinically in a sample of 21 keratoconus eyes with previous CXL surgery. In this sample, the value of $n_{k_{adj}}$ ranged from 1.3210 to 1.3306, which was consistent with the range found

in our theoretical simulations. No statistically significant differences were found between $P_{k_{adj}}$ and P_c^{Gauss}, with a very strong and statistically significant correlation between both values. The mean difference was +0.09 D, with 85% of cases showing a difference of 0.7 D or below and 76% of cases showing a difference of 0.5 D or below. Therefore, if r_{2c} is not available or cannot be measured, the keratometric approach can be used to estimate the corneal power in keratoconus eyes with previous CXL surgery with an acceptable error associated in most of cases. Similar results were obtained in our previous study in nontreated keratoconus corneas using a specific adjusted keratometric algorithm [5]. In such study, no statistically significant differences were also found between $P_{k_{adj}}$ and P_c^{Gauss}, with a mean difference of +0.04 D. Besides this analysis, we confirmed in the clinical sample that the classical keratometric approach based on the use of the corneal refractive index of 1.3375 provided a very significant overestimation of the corneal power, with a mean difference between $P_{k(1.3375)}$ and P_c^{Gauss} of +1.63 D. As in healthy corneas [1, 2] as well as in post-LASIK [3] and keratoconus corneas [4, 5], the keratometric value of 1.3375 is not valid for corneal power calculation in keratoconus eyes with previous CXL surgery.

There are some potential weaknesses in this study, such as the use of a limited number of theoretical eye models for the simulations or the use of paraxial optics, not considering the effect of corneal asphericity on ΔP_c. However, the purpose of the study was only to evaluate the error in the estimation of the central corneal power where paraxial optics can be applied without errors, which is the easiest and fastest procedure for the clinical practice. Regarding the clinical study, the sample size was limited and it can be considered as a preliminary study. However, it should be considered that it is the first study evaluating the error associated to keratometric approach for corneal power calculation in keratoconus eyes with previous CXL and the clinical results are completely consistent with those obtained in simulations. Future studies should be done to confirm our results with a larger number of cases as well as to evaluate the real benefit of using our adjusted algorithm for corneal power estimation in intraocular lens power calculation after CXL. Likewise, the potential usefulness of our algorithm in keratoconus eyes undergoing crosslinking using other different techniques (epi-off, iontophoresis) must be investigated.

In conclusion, the use of a single value of n_k for the estimation of the corneal power using the keratometric approach is not valid in eyes with keratoconus and previous CXL surgery and can lead to significant errors. Specifically, the use of the classical keratometric corneal refractive index of 1.3375 to estimate the corneal power using the keratometric assumption must be avoided as it leads to significant levels of overcorrection of corneal power. This can be minimized using a variable adjusted corneal refractive index ($n_{k_{adj}}$) if the technology required for the measurement of the posterior corneal curvature is not available. This variable corneal refractive index is dependent on the keratoconus stage. Changes in this algorithm due to post-CXL time should be also investigated in future studies.

Conflicts of Interest

The authors have no proprietary or commercial interest in the medical devices that are involved in this manuscript.

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