The Egyptian Journal of Hospital Medicine (April 2019) Vol. 75 (5), Page 2871-2877

Accelerated versus Conventional Corneal Collagen Cross-Linking in The Treatment of Keratoconus

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ABSTRACT

Background: corneal collagen cross-linking (CXL) is one of the interesting topics in corneal surgery, with several recent modifications of the original Dresden protocol under investigation. Accelerated CXL is one of the exciting modifications of the original technique but with few published results. It

Objective: the aim of the present study was to compare the effect of accelerated (both continuous and pulse) crosslinking on the keratoconic cornea versus conventional protocol. We stuck to inclusion and exclusion criteria of the study.

Patients and methods: in this study we evaluated 90 eyes; 30 eyes received standard Dresden protocol (S-CXL), 30 eyes received continuous light accelerated protocol (cl-ACXL), and 30 eyes received pulsed light accelerated protocol (pl-ACXL). The refractive status, visual acuity, corneal topography, central corneal thickness and corneal biomechanics were evaluated preoperatively, at 1st month, 3rd month, 6th month and 12th month postoperative.

Results: all groups showed an improvement of MRSE, UCVA and BCVA one year after surgery. The central corneal thickness (CCT) markedly decreased at 1st month follow-up, then gradually increased till 12th month but still below the baseline. Both maximum and minimum keratometry (K-max and K-min) decreased significantly at 12th month follow-up. The corneal biomechanics; corneal hysteresis (CH) and corneal resistance factor (CRF) showed no significant changes all over the follow-up period.

Conclusion: the results in this study showed that both continuous and pulsed light accelerated cross-linking are as safe as standard Dresden protocol in halting keratoconus disease.

Keywords: CXL, Keratoconus.

INTRODUCTION

Crosslinking is the general term for the process of forming covalent bonds or relatively short sequences of chemical (ionic) bonds to join two polymer chains together. When polymer chains are crosslinked, the material becomes more rigid. Cross-links can be formed by chemical reactions that are initiated by heat, pressure, change in pH, or radiation **(1).** Cross-linking of collagen refers to the ability of collagen fibrils to form strong chemical bonds with adjacent fibrils. In the cornea, collagen cross-linking occurs naturally with aging and as a side-effect of diabetes due to an oxidative deamination reaction that takes place within the end chains of the collagen. It was hypothesized that this natural cross-linkage of collagen explains why keratoectasia (corneal ectasia) often progresses most rapidly in adolescence or early adulthood but tends to stabilize in patients after middle-age **(2).**

Biomechanical investigation of human keratectatic corneas reveals significant differences in elasticity compared to normal corneas, indicating a decreased stiffness of the keratoconus cornea **(3).**

Corneal cross linking is steadily becoming part of routine care for early and moderate keratoconus. Hence, procedures are now being developed to address the residual refractive error and treatment of more advanced keratoconus. These procedures include combining corneal cross linking with other refractive modalities. However, some combination therapies such as excimer laser ablation and corneal cross linking remain controversial. Additionally, the indications for customized ablation and corneal cross linking remain unclear **(4).**

Developments in CXL procedure also showed using CXL with intrastromal pocket by femtosecond laser, one of its advantage was a novel epithelial sparing and no postoperative pain, as most patients returned to everyday activities without eye irritation or discomfort. Also cross-linking the sclera was tried, including treatment for malignant myopia, scleromalacia, and low-tension glaucoma. Adjunctive CXL with certain corneo-plastic procedures, including conductive keratoplasty to induce corneal steepening or microwave keratoplasty to induce corneal flattening, have shown promising results **(5).**

The caveat remains that corneal cross linking is a relatively new procedure that still requires extensive research and long-term follow-up **(4).**

AIM OF THE WORK

To evaluate the use of accelerated corneal collagen cross-linking (using pulse and continuous mode) in comparison with conventional cross-linking in the management of keratoconus.

PATIENTS AND METHODS

The study was conducted at Al-Hussein University Hospital, Department of Ophthalmology.

Received:8/2/2019
Accepted:10/3/2019

Patients:

A prospective comparative study that included 90 eyes divided into three groups:

- **Group (A):** 30 eyes treated with standard CXL.
- **Group (B):** 30 eyes treated with continuous light accelerated CXL.
- **Group (C):** 30 eyes treated with pulsed light accelerated CXL.
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Written informed consent.

An approval of the study was obtained from Al-Azhar University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

Inclusion criteria:

- Age: 16 – 40 years.
- A minimum pachymetry of 400 μm at the thinnest corneal location.
- Keratoconus grade 1 and 2 according to Amsler-Krumeich classification.
- No previous ocular surgery.
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Exclusion criteria:

- Age: <16 or >40 years.
- Thinnest corneal pachymetry less than 400 μm.
- Keratoconus grade 3 and 4 according to Amsler-Krumeich classification.
- Patients with corneal opacity or hydrops.
- Pregnancy.
- Diabetes Mellitus.
- History of herpetic keratitis.
- Moderate to severe dry eye.
- Autoimmune diseases.

Preoperative evaluation:

All patients had undergone the following examinations:

- Slit-lamp biomicroscopy.
- Manifest refraction spherical equivalent (MRSE).
- Uncorrected visual acuity (UCVA).
- Best corrected visual acuity (BCVA).
- Central corneal thickness (CCT) measured by Orbscan IIz (Bausch & Lomb, Rochester, NY, USA).
- Maximum and minimum keratometry (K-max and K-min) measured by Orbscan IIz.
- Corneal hysteresis (CH) and corneal resistance factor (CRF) measurements by ocular response analyzer (ORA; Reichert Ophthalmic Instruments, Buffalo, NY, USA) (Figure 1B).

The procedure:

The corneal epithelium was scrapped using hockey knife after applying Merocel sponge soaked in benoxinate 0.4% for 30 seconds (Figure 1).

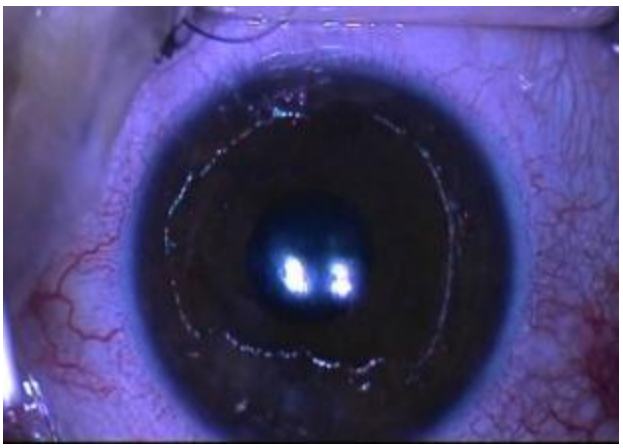

Figure (1): A studied case showing removal of corneal epithelium prior to CXL.

In group (A), a drop of riboflavin 0.1% with hydroxypropyl methylcellulose (VibeX Rapid™; Avedro, Inc.) was applied every 2 minutes for 10 minutes, followed by exposure to ultraviolet light (365 nm, 3 mW/cm^2) for 30 minutes using XLink™ system (Opto, Inc.) during which riboflavin was applied every 5 minutes. This corresponds to a total radiant exposure of 5.4 J/cm^2.

In group (B), a drop of riboflavin 0.1% with hydroxypropyl methylcellulose (VibeX Rapid™; Avedro, Inc.) was applied every 2 minutes for 10 minutes, followed by exposure to ultraviolet light (365 nm, 30 mW/cm^2) in continuous mode for 4 minutes using the KXL® system (Avedro, Inc.) during which riboflavin was not applied. This corresponds to a total radiant exposure of 7.2 J/cm^2.

In group (C), a drop of riboflavin 0.1% with hydroxypropyl methylcellulose (VibeX Rapid™; Avedro, Inc.) was applied every 2 minutes for 10 minutes, followed by exposure to ultraviolet light (365 nm, 30 mW/cm^2) in pulse mode (1 sec on + 1 sec off) for 8 minutes using the KXL® system (Avedro, Inc.) during which riboflavin was not applied. This corresponds to a total radiant exposure of 7.2 J/cm^2.

Care was taken to protect the limbus from inadvertent ultraviolet exposure in all groups. Finally, a bandage contact lens was applied, and a topical antibiotic (gatifloxacin 0.3%) and a topical lubricant (carboxymethylcellulose sodium 1.0%) was prescribed.

Postoperative follow-up:

The patients were followed up for one year (1st month, 3rd month, 6th month and 12thmonth) by:

- Slit-lamp biomicroscopy.
- Manifest refraction spherical equivalent (MRSE).
- Uncorrected visual acuity (UCVA).
- Best corrected visual acuity (BCVA).
- Central corneal thickness (CCT) measured by Orbscan IIz.

- Maximum and minimum keratometry (K-max and K-min) measured by Orbscan IIz.
- Corneal hysteresis (CH) and corneal resistance factor (CRF) measurements by Ocular Response Analyzer (ORA).
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Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following:
- Probability (P-value)
- P-value <0.05 was considered significant.
- P-value <0.001 was considered as highly significant.
- P-value >0.05 was considered insignificant.

RESULTS

Demographic data:

This study included 90 eyes divided into three groups, group (A) included 30 eyes who underwent standard cross-linking (S-CXL), group (B) included 30 eyes who underwent continuous light accelerated cross-linking (cl-ACXL), and group (C) included 30 eyes who underwent pulsed light accelerated cross-linking (pl-ACXL).

Age distribution in S-CXL group was 25.37 ± 5.61, cl-ACXL group was 24.50 ± 4.98, and pl-ACXL group was 26.27 ± 5.40. Gender distribution in S-CXL group was 13 (43%) male patients and 17 (57%) female patients, cl-ACXL group was 16 (53%) male patients and 14 (47%) female patients, and pl-ACXL group was 14 (47%) male patients and 16 (53%) female patients.

There was no statistical difference between the three groups in terms of demographics, preoperative MRSE, UCVA, BCVA, K-max, CCT and CRF. However, the cl-ACXL group had a significantly higher preoperative CH than S-CXL and pl-ACXL groups. On the other hand, the S-CXL group had a significantly lower preoperative K-min than cl-ACXL and pl-ACXL groups (Table 1).

Table (1): Comparison of baseline parameters between the studied groups.

	S-CXL (N=30)	cl-ACXL (N=30)	pl-ACXL (N=30)	P-value
Age (years)	25.37 ± 5.611	24.50 ± 4.981	26.27 ± 5.401	0.443
Sex (male:female)	13:17	16:14	14:16	0.732
MRSE (D)	-3.94 ± 1.829	-3.42 ± 1.775	-3.76 ± 1.265	0.470
UCVA (LogMAR)	0.773 ± 0.324	0.673 ± 0.357	0.793 ± 0.199	0.261
BCVA (LogMAR)	0.310 ± 0.134	0.253 ± 0.152	0.293 ± 0.101	0.234
CCT (µm)	500.13 ± 45.84	514.03 ± 57.97	504.4 ± 40.2	0.527
K-max (D)	48.59 ± 2.26	48.42 ± 2.31	48.78 ± 1.891	0.806
K-min (D)	44.58 ± 1.858	45.82 ± 1.863	45.78 ± 2.146	0.024
CH (mmHg)	7.75 ± 1.11	8.51 ± 0.89	7.96 ± 1.33	0.032
CRF (mmHg)	7.06 ± 1.26	7.707 ± 1.12	7.700 ± 1.062	0.050

Visual acuity and refractive outcomes:

On comparing the three groups, the P value at 1st, 3rd, 6th and 12th month from baseline was 0.281, 0.827, 0.225 and 0.166 respectively which showed no statistically difference between the studied groups (Table 2).

Table (2): Comparison of MRSE change between groups.

MRSE	Sum of Squares	Mean Square	F	Sig.
1st Month - Pre *(Between Groups)*	1.318	0.659	1.288	0.281
3rd Month - Pre *(Between Groups)*	0.235	0.117	0.190	0.827
6th Month - Pre *(Between Groups)*	0.579	0.290	1.520	0.225
12th Month - Pre *(Between Groups)*	0.467	0.233	1.831	0.166

On comparing the three groups, the P value at 1st, 3rd, 6th and 12th month from baseline was 0.844, 0.899, 0.131 and 0.227 respectively which showed no statistically difference between the studied groups (Table 3).

Table (3): Comparison of BCVA change between groups.

BCVA	Sum of Squares	Mean Square	F	Sig.
1st Month - Pre *(Between Groups)*	0.003	0.001	0.170	0.844
3rd Month - Pre *(Between Groups)*	0.002	0.001	0.107	0.899
6th Month - Pre *(Between Groups)*	0.020	0.010	2.080	0.131
12th Month - Pre *(Between Groups)*	0.011	0.005	1.510	0.227

Pachymetric outcomes:

On comparing the three groups, the P value at 1st, 3rd and 6th month from baseline was 0.423, 0.074 and 0.138 respectively which showed no statistically difference till the 6th month follow up. However, the pl-ACXL group showed a significant more reduction at 12th month (P=0.045) (Table 4).

Table (4): Comparison of CCT change between groups.

CCT	Sum of Squares	Mean Square	F	Sig.
1st Month - Pre *(Between Groups)*	2350.689	1175.344	0.868	0.423
3rd Month - Pre *(Between Groups)*	5543.489	2771.744	2.677	0.074
6th Month - Pre *(Between Groups)*	1308.822	654.411	2.023	0.138
12th Month - Pre *(Between Groups)*	1010.022	505.011	3.204	0.045

Topographic outcomes:

On comparing the three groups, the P value at 1st, 3rd, 6th and 12th month from baseline was 0.987, 0.900, 0.689 and 0.622 respectively which showed no statistically difference between the studied groups (Table 5).

Table (5): Comparison of K-max change between groups.

K-max	Sum of Squares	Mean Square	F	Sig.
1st Month - Pre *(Between Groups)*	0.033	0.016	0.013	0.987
3rd Month - Pre *(Between Groups)*	0.278	0.139	0.105	0.900
6th Month - Pre *(Between Groups)*	0.375	0.187	0.374	0.689
12th Month - Pre *(Between Groups)*	0.266	0.133	0.477	0.622

On comparing the three groups, the P value at 1st, 3rd, 6th and 12th month from baseline was 0.601, 0.903, 0.432 and 0.514 respectively which showed no statistically difference between the studied groups (Table 6).

Table (6): Comparison of K-min change between groups.

K-min	Sum of Squares	Mean Square	F	Sig.
1st Month – Pre *(Between Groups)*	1.122	0.561	0.513	0.601
3rd Month - Pre *(Between Groups)*	0.149	0.074	0.102	0.903
6th Month - Pre *(Between Groups)*	0.755	0.377	0.848	0.432
12th Month - Pre *(Between Groups)*	0.434	0.217	0.672	0.514

➢ **Biomechanical outcomes:**

On comparing the three groups, the P value at 1st, 3rd, 6th and 12th month from baseline was 0.354, 0.207, 0.886 and 0.606 respectively which showed no statistically difference between the studied groups (Table 7).

Table (7): Comparison of CH change between groups.

CH	Sum of Squares	Mean Square	F	Sig.
1st Month - Pre ***(Between Groups)***	1.171	0.585	1.050	0.354
3rd Month - Pre ***(Between Groups)***	1.740	0.870	1.602	0.207
6th Month - Pre ***(Between Groups)***	0.127	0.063	0.121	0.886
12th Month - Pre ***(Between Groups)***	0.769	0.384	0.504	0.606

On comparing the three groups, the P value at 1st, 3rd, 6th and 12th month from baseline was 0.516, 0.641, 0.336 and 0.530 respectively which showed no statistically difference between the studied groups (Table 8).

Table (8): Comparison of CRF change between groups.

CRF	Sum of Squares	Mean Square	F	Sig.
1st Month - Pre ***(Between Groups)***	0.713	0.356	0.668	0.516
3rd Month - Pre ***(Between Groups)***	0.621	0.310	0.447	0.641
6th Month - Pre ***(Between Groups)***	1.350	0.675	1.106	0.336
12th Month - Pre ***(Between Groups)***	0.998	0.499	0.640	0.530

DISCUSSION

Refractive status and visual acuity outcomes:

In this study, all groups showed a myopic shift at 1st month after surgery. The MRSE started to improve gradually at 3rd month till 12th month follow up. There was a statistically significant improvement of MRSE at 6th and 12th months. The change in MRSE at 12th month was 0.67 ± 0.34, 0.50 ± 0.30 and 0.54 ± 0.41 diopter units for S-CXL, cl-ACXL and pl-ACXL groups respectively.

In 2014, Tomita and his colleagues[6] conducted a study to compare the effect of S-CXL (18 eyes) and cl-ACXL (30 eyes). They showed an improvement of MRSE in both groups at 1st year follow up. The change in MRSE was 0.39 ± 0.88 and 0.64 ± 1.84 in both S-CXL and cl-ACXL groups respectively.

The improvement in MRSE in the present study is somewhat similar to their results. However, their study included a smaller number of eyes regarding the S-CXL group.

The change in MRSE is comparable to their results. However, their accelerated protocol was (18 mW/cm^2 for 5 minutes) which has less power intensity than the present accelerated protocol.

In 2017, Woo and his colleagues[7] conducted a study to compare MRSE outcomes of S-CXL and cl-ACXL after one-year follow-up. The S-CXL group showed no change in MRSE throughout follow-up, but in the cl-ACXL group, the subjects had a significantly more myopic MRSE compared to baseline at 1st month and 3rd month only. There was no significant change in MRSE from baseline at 12th month in the cl-ACXL group.

Their results differed from the present study. This is probably due to short time (3 days) discontinuation of subject's rigid gas permeable (RGP) contact lens before the screening visit.

In 2017, Jiang and his associates[8] compared the pl-ACXL to the S-CXL in terms of MRSE. At the 12th month, there were no statistically significant differences in postoperative MRSE between the S-CXL and pl-ACXL groups. Furthermore, no statistically significant differences were detected in the MRSE between the postoperative and baseline values in the two groups.

Their study showed a similar result to the present study regarding the difference between both groups at 12th month. However, their result differed regarding the difference between 12th month to baseline. This may be attributed to higher keratoconus grade subjects (1-3 according to Amsler-Krumeich classification) included in their study.

In this study, all groups showed a noticeable deterioration in UCVA and BCVA at 1st month after surgery. Later on, they gradually improved at 3rd month till reached peak at 12th month. There was a statistically significant improvement of both UCVA and BCVA at 6th and 12th months follow up. The change in UCVA after one year was -0.18 ± 0.15, -0.13 ± 0.11 and -0.19 ± 0.12, while the change in BCVA was -0.10 ± 0.07, -0.07 ± 0.05 and -0.10 ± 0.05 for S-CXL, cl-ACXL and pl-ACXL groups respectively.

In 2014, Tomita and his colleagues[6] conducted a study to compare the effect of cl-ACXL to S-CXL in terms of UCVA and BCVA. They showed an improvement in both values one year after surgery. There were no statistically significant differences in postoperative UCVA and BCVA between the cl-ACXL and the S-CXL groups.

Their result is similar to this study. However, they used a different riboflavin in each group (Isotonic 0.1% riboflavin with HPMC for cl-ACXL group and Isotonic 0.1% riboflavin with 20.0% dextran T500 for the S-CXL group), which makes this study more accurate as we used the same type of riboflavin.

In 2017, Jiang and his associates [8] conducted a comparative study between the S-CXL and the pl-ACXL. At the 12th month follow-up, both UCVA and BCVA demonstrated a statistically significant improvement in the S-CXL and pl-ACXL groups.

This study showed similar result to **Jiang *et al.* [8]** study, but it was less accurate as they used different types of riboflavin in each group (0.1% riboflavin solution in 20% dextran for S-CXL and 0.1% riboflavin with HPMC for pl-ACXL).

In 2017, Woo and his colleagues[7] showed that in the S-CXL group, there was significant improvement in the UCVA from baseline at 3rd month and 6th month. In addition, the BCVA showed a significant improvement from baseline at 12th month. In the cl-ACXL group, there was no statistically significant change in UCVA throughout follow-up, with improvement in BCVA seen at 6th month and 12th month. There was no statistically significant difference in the change in both UCVA and BCVA from baseline between the two groups at 12th month follow-up.

Their results were somewhat similar to this study. However, they included some subjects with less than 400µm corneal thickness in the S-CXL group. In addition, they used different type of riboflavin between studied groups (Isotonic riboflavin 0.1% with dextran 20% for the S-CXL group and dextran-free riboflavin 0.1% for the cl-ACXL group).

Pachymetric outcomes:

In this study, all groups showed a decrease in CCT throughout the entire follow-up period. The peak was at 1st month after surgery which then gradually improved till the 12th month. However, the CCT remains slightly lower than the baseline one year after surgery.

The results of current study agreed with **Chow *et al.* [9]** who reported a reduction of CCT in S-CXL and cl-ACXL groups at one-year follow-up. In addition, the study showed no statistically difference between both groups.

However, the results of **Woo *et al.* [7]** are opposite to the results of the current study regarding CCT as they reported no significant change in from baseline at 12th month for both S-CXL and cl-ACXL. In addition, there was no significant difference in CCT change at 12th month between the two groups. This may be attributed to different riboflavin solutions and different soaking time used in both groups.

Topographic outcomes:

In this study, all groups showed a significant reduction in K-max at 6th month and 12th month follow-up. In addition, the K-min showed a significant reduction throughout the entire follow-up period. There was no statistically significant difference between the studied groups.

In 2015, Chow and associates[9] compared the K-max and K-min outcomes between the S-CXL and cl-ACXL. After one-year follow-up, there was a statistically reduction of K-max and K-min in the S-CXL group. The reduction in the cl-ACXL group was not statistically significant. However, there was no inter-group differences in the changes of keratometric values between S-CXL and cl-ACXL at one-year postoperatively.

Their different results may be attributed to short time discontinuation of subject's RGP contact lens before screening time (3 days).

Biomechanical outcomes:

In current study, all groups showed no significant change in CH and CRF throughout the entire follow-up period. In addition, there was no statistically significant difference between the studied groups in both CH and CRF.

These results are similar to that of **Tomita *et al.* [6] and Hashemi *et al.* [10]** who conducted a study to compare cl-ACXL to S-CXL. They reported no statistically significant differences in the changes of corneal biomechanical response (CH and CRF) either after one-year from baseline or between the two groups.

Despite the fact of increased mechanical rigidity in human corneas proved by **Wollensak *et al.* [11]**, both **Piñero and Alcón [12]** suggested that the two biomechanical values (CH and CRF) are not useful for analyzing in detail the biomechanical changes occurring after CXL in vivo. This supports the results of the current study.

Woo *et al.* [7] found a significant improvement in CH and CRF from baseline in the cl-ACXL group at 12th month. For the S-CXL group, there was no significant change in the CH and CRF between baseline and up to the 12th month.

Their results were different than the present study. They showed a significant increase of CH and CRF in the cl-ACXL group. However, this may be attributed to a relatively higher number of their subjects in the cl-ACXL group (N=29 for S-CXL and N=47 for the cl-ACXL).

CONCLUSION

The results in this study showed that both continuous and pulsed light accelerated cross-linking

are safe and effective procedures for management of keratoconus.

The final results revealed no statistically significant difference between the standard and accelerated (both continuous and pulsed) cross-linking protocols in terms of: manifest refraction spherical equivalent, uncorrected visual acuity, best corrected visual acuity, central corneal thickness, maximum keratometry, minimum keratometry, corneal hysteresis and corneal resistance factor.

There is no statistically significant difference between accelerated pulsed and continuous corneal cross-linking.

The current study proved that both continuous and pulsed light accelerated protocols are a time saving procedure for halting keratoconus.

RECOMMENDATIONS

- As infection may occur post CXL, the procedure should be performed under complete aseptic conditions and in an operating room.
- Also, special care for post CXL contact lens wear, to avoid any related complications.
- All patients should be examined thoroughly for any systemic and local eye diseases with an adequate history taking.
- Using the continuous light accelerated protocol is the best choice, as it has the shortest interventional time with the best patient compliance and less incidence of post-operative complications.

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