Processed Tissue Customization: Development of an Operator-Specific Nomogram for Eye Bank Pre-cut Tissue for DSAEK

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Eye banks have been processing corneal tissue for endothelial keratoplasty (EK) since 2005.[1] Preparation of DSAEK grafts by eye banks has been shown to create efficiencies for surgeons without impacting visual outcomes for patients.[2] Iowa Lions Eye Bank (ILEB) began supplying pre-cut tissue for EK in early 2006.

The eye bank's processing objective is to provide a posterior graft approximately one-fifth of the cornea's initial thickness to the transplanting surgeon. Processing of EK tissue involves the following abbreviated steps: 1) an operator performs a surgical scrub and enters the processing room, typically containing a laminar flow hood, 2) the cornea to be processed is introduced to a sterile field, mounted on an artificial anterior chamber and back-pressure is supplied by media or air, 3) microkeratome head size is selected to acquire the desired graft thickness as determined by pachymetry, using either a hand-held pachymeter or prior to processing by optical coherence tomography (OCT), with the selected microkeratome head size then mounted on a motorized turbine, 4) the microkeratome is mounted on a post or between two slides and the tissue is cut to the desired depth, 5) an approximately 10.0 mm anterior layer is removed from the microkeratome head and placed back on the stromal bed after moisture is wicked away. Moria Inc., the manufacturer of the microkeratome in use at ILEB, provides a user's manual which includes the incremental values for the cutting depth of each of the 250µ (actual is 310µ), 300µ (actual is 370µ) and 350µ (actual is 435µ) microkeratome heads.[3] Initially, those preparing tissue used the manufacturer's recommendations to choose the microkeratome head to achieve the thickness desired by surgeons. (Fig. 1)

Initially, ILEB's Standard Operating Procedures (SOPs) stated graft thickness goal of 150 µ + 75 µ met most surgeon's needs. As research on graft thickness and visual outcomes became available4, surgeon preference

Thickness of Cornea	Action	Cutting Head
< 425 microns	do not cut	n/a
425-475 microns	leave Epithelium on	250 µ
475-525 microns	remove Epithelium	250 µ
525-575 microns	leave Epithelium on	300 µ
575-600 microns	remove Epithelium	300 µ
600-625 microns	leave Epithelium on	350 µ
625-675 microns	remove Epithelium	350 µ
> 675 microns	likely not acceptable (too thick)	n/a

Fig. 1 *Early nomogram based on information found in the Moria microkeratome equipment manual. This nomogram details which microkeratome cutting head should be selected and whether or not to keep or remove the epithelium based on the initial thickness measurements of the cornea. In the case of "do not cut" the indication is the tissue is already too thin and may lead to greater likelihood of tissue perforation.*

for thinner tissue became more widespread, the SOP was revised to 125 µ, with the acceptable range continued at + 75 µ. Surgeons have grown to rely on the eye bank's ability to process tissue with tighter ranges than + 75 µ, as they seek to achieve the maximum visual outcome for their patients.[4]

In 2009, ILEB reported an average posterior layer graft thickness of 153 + 28 µ. The low standard deviation demonstrates the eye bank's ability to process tissue in an accurate and consistent manner.[5] Currently, many surgeons are requesting thinner tissue and ultra-thin DSAEK grafts due to improvements in visual outcomes.[6,7] As surgeon requests continue trending toward thinner grafts, the eye bank's ability to process tissue within a narrow surgeon dictated range could mean the difference between an unacceptably thick graft and perforating the tissue.

Eye banks must meet surgeon specifications to place tissue. To accurately cut to specified depths, the operator may choose to employ a variety of strategies. Prior to processing, the donor cornea epithelium may also be removed or left in place to augment depth of cut control. The eye bank may choose to increase or decrease pressure behind the cornea while mounted in the artificial anterior chamber or to increase or decrease the speed of which the cutting head passes over the tissue. Despite the ability to alter the pressure and speed as well as epithelium removal, increasing the ability to achieve the desired graft thickness through decreasing the standard deviation remained a goal at ILEB. This decreases the margin of error for the operator allowing ultrathin grafts to be prepared while eliminating the need for additional processing such as occurs with the double-pass technique, to achieve the desired graft thickness.[8,9,10]

METHOD

ILEB documented tissue processing outcomes for six different data points, to create a nomogram personalized to each operator according to each individual cutting head. The six data points considered were derived from the action and cutting head indicated by the manufacturer-derived nomogram. (Fig. 1) The personalized nomogram project was conducted in two phases, the first being an individual operator nomogram reference on paper. This chart was specific to each of the three operators based on the outcomes used with each microkeratome head, but was not specific to each microkeratome system. The second phase was specific to the operator and specific to each microkeratome system. The number of data points to accomplish the second phase required the nomogram to be automated utilizing Microsoft Excel. An initial study of tissue processing outcomes was conducted using the first phase of the personalized nomogram from August 2011 through May 2012 for the three operators (n=590). Utilizing the paper individualized nomogram, the study demonstrated the operator's average standard deviation of the processed posterior layer was within +15 µ of the desired goal.

At the time the operator-specific nomogram project began, ILEB was utilizing three complete Evolution 3 Moria CB microkeratome systems manufactured by Moria, Inc. Each system consisted of three microkeratome heads: 250 µ, 300 µ and 350 µ. There were four operators authorized to process EK tissue, resulting in 36 different nomograms to be developed. Each operator had slight variances in the way they processed tissue, resulting in different cut depths using the same equipment. Each of the nine microkeratome heads was calculated separately due to slightly different standard deviations from the expected cutting depth.

Full-thickness pachymetry by OCT was collected for all tissues and assigned to one of the six categories of operator instruction according the new nomogram. These included cutting with each microkeratome head and leaving the epithelial layer intact or removing the epithelial layer.

All processing parameters were gathered for four operators to determine the eye bank average. Individual microkeratome head averages were utilized only when an operator had performed a minimum of 100 cuts with each head. If 100 cuts had not been performed with a particular head by an operator, the overall eye bank average was used to create their personalized nomogram. Next, cutting depth averages were calculated for each operator for each microkeratome head. This average was then used to re-create the eight data points depicted in the nomogram from Fig. 1. The result is 96 data decision points to create personalized nomograms for four operators.

Surgeons request various graft thicknesses, according to their own preferences. Based on surgeon request history, ILEB determined the most common nomograms would be for goals of 75 µ, 85 µ, 100 µ, 125 µ and 150 µ. The result is 480 data decision points which, for ease of use, resulted in the creation of a table utilizing Microsoft Excel. The data decision points were placed in the background and a user interface was established so that for each tissue only the entry of the operator, cut depth goal, microkeratome head identification, initial pachymetry and tissue identification number was required. (Fig. 2) The output gives the user the action (leave epithelium, remove epithelium or recommend not cutting) and the head selection. (Fig. 3) Specific corneal tissues still require consideration of additional factors other than those entered in the nomogram. The surgeon's preference, such as erring on the side of a thinner or thicker graft, may influence a decision to make a change from the nomogram's prescribed action in order to meet the surgeon's needs. To achieve the best possible outcome for a specific goal, the user has the option of re-applying the nomogram to select a different microkeratome head. For example, the 250µ head from kit 1 produces a different result from the 250µ head from kit 2 or kit 3. By selecting a specific microkeratome head, equipped with knowledge of that head's properties, the operator can further refine results to achieve the desired outcome.

The date of death to the date of processing interval is considered in the "date of death to date of cut" (DTC) box. The thickness of the corneal epithelium in storage conditions decreases in correlation to the amount of time spent in media,11,12 and epithelial thickness will impact final outcomes when epithelium is removed prior to processing. OCT analysis from the same nomogram data set was used to determine epithelial thickness in an eye bank setting

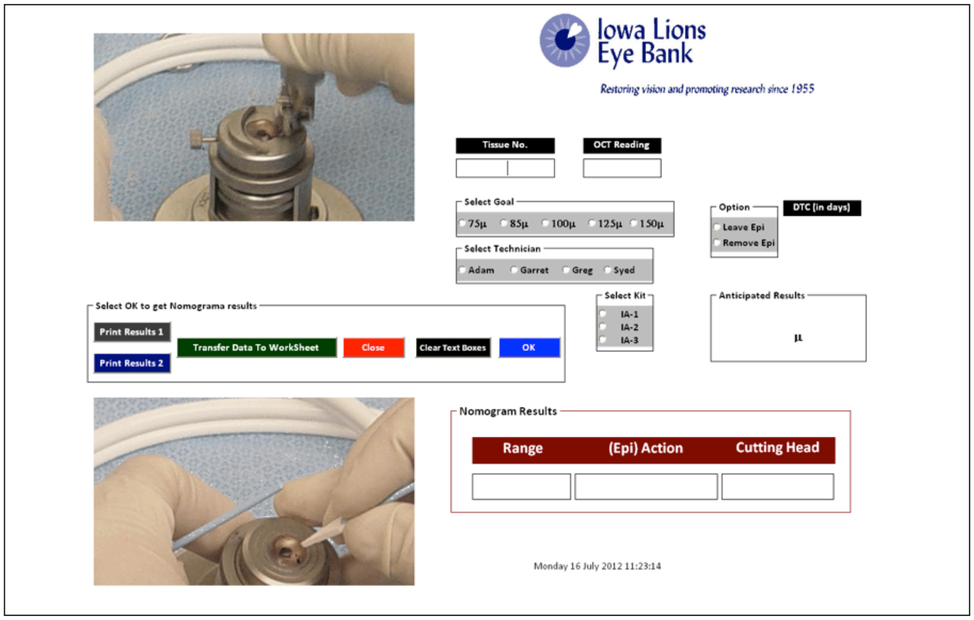

Fig. 2 Screenshot of the ILEB personalized nomogram's operator interface. The operator will enter the tissue number, OCT reading, goal thickness, technician name and kit number. By clicking "OK" the results will be generated and the user can obtain the anticipated result after entering the "DTC" or duration of days to cut and decision to leave the epithelium or remove it. At this point, the goal thickness or kit number can be amended to yield the best case anticipated result.

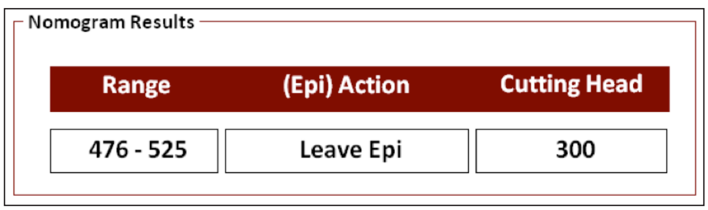

Fig. 3 Sample results generated by entries made in the ILEB personalized nomogram operator interface.

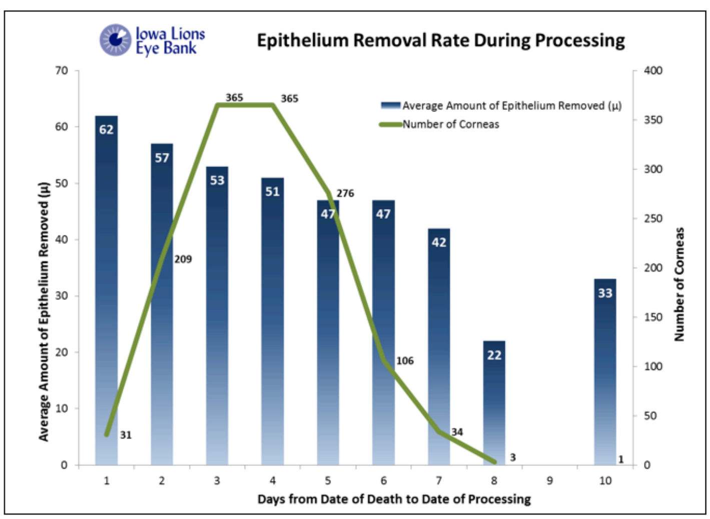

Fig. 4 Demonstrates the average amount of epithelium removed from donor corneas at ILEB according to how many days after death processing occurred. Epithelial thickness decreased with time. Day 10 was an outlier (n=1) and most corneas were processed between days 2 and 5.

related to the number of days from donor death to processing. (Fig. 4) This average is used as additional input in the nomogram program to calculate the anticipated final depth of the cut. (Fig. 5)

Data feedback for this study was tabulated utilizing outcomes from an operator whose ability to perform a consistent cut routinely and the ability to manage additional factors during processing increased over time with experience.

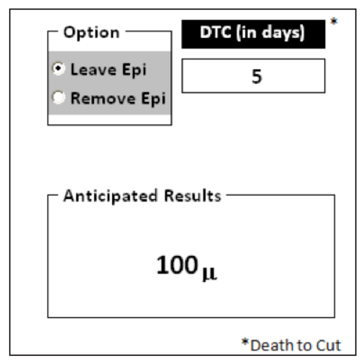

Fig. 5 Data from figure 4 was used to calculate the anticipated results in the ILEB personalized nomogram. This information allows the operator to exchange kits, change decision to leave/remove epithelium or make further adjustments during processing to obtain results closer to the goal thickness.

RESULTS

1702 eye bank pre-cut corneas for DSAEK between May 2012 and December 2014 were analyzed. Tissues were omitted where the nomogram prescribed not cutting the tissue as it was "likely too thick" (n=10). In these cases, attempts to make the cut were performed at the surgeon's discretion and the operators were able to achieve acceptable graft thickness in all ten.

Full-thickness pachymetry by OCT was collected for all tissues and assigned to one of the six categories of operator instruction according the new nomogram. These included cutting with each microkeratome head and leaving the epithelial layer intact or removing the epithelial layer. Fig. 6 shows the average cornea thickness for each of the prescribed cutting instructions, along with the minimum and maximum thickness and standard deviation. The standard deviation was the largest for the 350 µ microkeratome head at 28 µ and a range of 166 µ. The smallest deviation occurred with the 250 µ microkeratome head at 19 µ and a range of 85 µ. The operator-specific nomogram has given the operator the ability to more closely achieve the target posterior layer thickness.

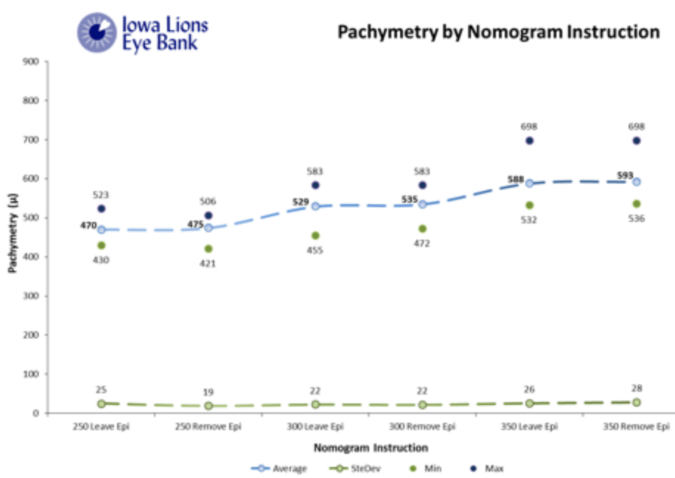

Fig. 6 *Data shows the average thickness with minimum/maximum and standard deviation as categorized by each type of instruction provided by the ILEB personalized nomogram.*

The automated nomogram provides the operator with an anticipated posterior layer thickness based on all of the decision points and improves the ability of the tissue processing operator to achieve the desired outcome of the cut. The standard deviation across all nomogram instructions revealed similar outcomes with a range of only 10 µ – 14 µ (Fig. 7). The minimum for each decision point is zero, representing a cut that resulted in the exact anticipated thickness. The standard deviation increased with each microkeratome head from 250 µ to 350 µ.

The average overall standard deviation was + 12 µ. This compares favorably with the reported standard deviation prior to the use of the new nomogram, which was 28 µ.[5]

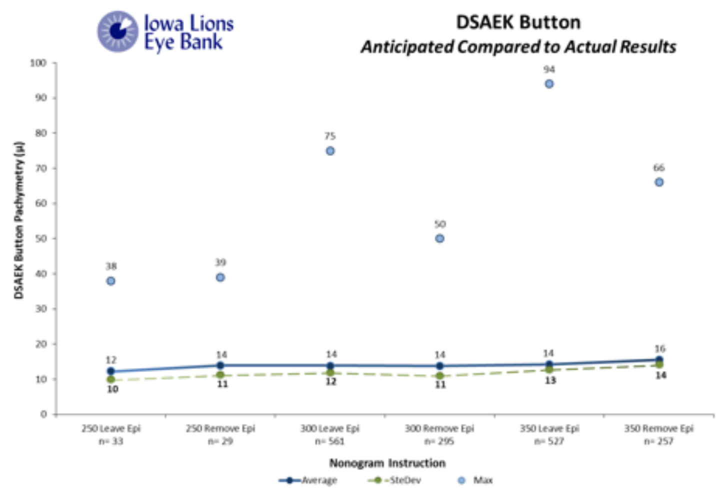

Fig. 7 *Compares the anticipated results estimated by the ILEB personalized nomogram to the actual results received upon post-processing OCT evaluation. Maximum values are represented as absolute values. Standard deviation across the all nomogram instructions ranges from 10-14µ.*

COMMENTS

This study demonstrates that a surgeon requested posterior layer thickness can be achieved with a small deviation using an operator and equipment specific nomogram that considers OCT readings and the impact of epithelial thickness as a result of time in storage media. The larger the microkeratome head, the greater the standard deviation.

The trend in surgeon requests has moved towards thinner grafts, including ultra-thin grafts, defined as a posterior layer under 100 µ.6,7 This study demonstrates one eye bank's process to increase the frequency with which the targeted thickness request is achieved, thereby proactively preventing potential tissue loss at the eye bank should surgeons reject tissue they find unsatisfactory.

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