Comparison of Graft Outcomes Reusing Original Intermediate-Term Cold Storage Solution for Entire Corneal Donor Storage Period With Exchanged Fresh Storage Solution After Donor Preparation in the Cornea Preservation Time Study

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Purpose: The purpose of this study was to evaluate outcomes of Descemet stripping automated endothelial keratoplasty comparing exchange with fresh intermediate-term cold storage solution after reuse of the original intermediate-term cold storage solution.

Results: The 3-year graft success rate (95% confidence interval) was 93.4% (90.7%–95.3%) in the Fresh group and 95.2% (91.8%–97.2%) in the Original group (adjusted hazard ratio for graft failure = 0.64, 95% confidence interval, 0.33–1.24, P = 0.19). The mean percentage endothelial cell loss was significantly greater in the Fresh group versus Original group (45% ± 22% vs. 38% ± 20%, respectively, P = 0.004). Cultures were positive in 4 (1.5%) of 267 donor rims (3 fungal and 1 bacterial) in the Fresh group and in 4 (2.5%) of 158 in the Original group (P = 0.57). There were 2 postoperative infections in the Original group and none in the Fresh group.

Conclusions: The use of the original intermediate-term cold storage solution did not reduce the 3-year graft success rate compared with exchanging with fresh solution after lenticule preparation for Descemet stripping automated endothelial keratoplasty, while the frequency of positive donor rim cultures did not significantly differ between groups.

Key Words: intermediate-term cold corneal donor storage solution, endothelial keratoplasty, graft outcomes

Intermediate-term cold storage between 2 and 8°C with Federal Drug Administration (FDA)-approved solutions up to 14 days has been the principal storage method for eye banks in the United States since the 1990s. Supporting this storage period, comparable graft outcomes for Descemet stripping automated endothelial keratoplasty (DSAEK) were reported out to 11 days with the Cornea Preservation Time Study (CPTS).1,2 With this time frame widely adopted for this
procedure as well as for penetrating keratoplasty (PKP) and Descemet membrane endothelial keratoplasty (DMEK). There are currently 4 FDA-approved intermediate-term storage solutions approved for the US market: OptiSol GS (Bausch and Lomb, Bridgewater, NJ), Life 4°C (NuMedis, Isanti, MN), and Eusol-C and Kerasave (Alchimia, San Nicolò, Italy). These storage solutions were originally developed for PKP with maintenance of the corneoscleral rim in solution for the entire storage period right up to the PKP. Because endothelial keratoplasty (EK) procedures became more popular over the past 15 years, the eye banks assumed an increasing role in the preparation of the lenticule and in the past 5 years loading the lenticule into the surgeon-preferred injector for efficient placement of the lenticule into position intraoperatively. As eye bank DSAEK procedures were developed, many eye banks elected to use the original storage solution during processing to fill the artificial anterior chamber instead of an alternate fluid such as balanced salt solution, necessitating the use of fresh solution for storage after processing. With subsequent concerns about contamination and endothelial health, many eye banks have incorporated into their standard operating procedure to replace the storage solution with fresh storage solution after tissue processing. There, however, have been no studies of the value for long-term graft outcomes with the exchange with fresh solution.

The need for such a study has recently become most pressing with the announcement by the Eye Bank Association of America of the closure of NuMedis production of Life 4°C and delays in the production and shipment of OptiSol GS by Bausch and Lomb in April 2022. In response, all eye banks in the United States institutes measures to conserve their supplies including 1) stricter criteria for recoveries to achieve higher percentage of transplantable donor tissue, 2) temporary reduction of international export of transplantable donor tissue, and 3) fewer recoveries for research and education. Eye banks currently exchanging the original solution with fresh solution at the time of lenticule preparation and/or injector insertion for preloaded cases have also considered no longer performing the exchange and instead reusing the original solution for both DSAEK and DMEK cases. This alteration in procedure could result in significant savings of solution usage for eye banks performing substantial EK lenticule preparation and preloading activity.

The CPTS was a randomized clinical trial that evaluated the effects of storage time or preservation time (PT) on graft success and endothelial cell loss (ECL) after DSAEK involving 1330 donor corneas from 23 eye banks enrolled between April 2012 and April 2014. One donor parameter that was prospectively gathered was whether the donor cornea was stored in the original storage solution for the entire storage period including after lenticule preparation or whether fresh solution was used after lenticule preparation. This data set then serves as an opportunity to explore this donor procedural difference on graft outcomes to support or dissuade the use of original storage solution throughout the entire storage period to conserve solution and reduce cost now and in the future, even when the current storage solution shortage is resolved.

This report compares the 3-year graft success rate and percentage of ECL for surviving clear grafts for those donor corneas stored in the original storage solution to those where the storage solution was exchanged for fresh solution. Because of the concern for contamination during lenticule preparation and reuse of original storage solution, donor rim culture positivity and the number of postoperative infections for the 2 groups were also examined.

**MATERIALS AND METHODS**

Details of the CPTS protocol have been previously reported including all donor, recipient, eye bank, operative, and postoperative parameters prospectively collected. The protocol required use of an FDA-approved intermediate-term cold storage solution. The protocol was approved by institutional review boards governing each investigational site, and individual participants gave written informed consent to participate in this study. Study oversight was provided by an independent data and safety monitoring committee. The research adhered to the tenets of the Declaration of Helsinki. The protocol was registered and is publicly available at https://clinicaltrials.gov/ct2/show/NCT01537393.

Participants were enrolled at 40 clinical sites, and donor corneas were provided by 23 eye banks. Eyes undergoing DSAEK were randomly assigned to receive a donor cornea with PT of 0 to 7 days or 8 to 14 days. The 1330 eyes completing surgery with a CPTS-assigned cornea were considered the “study eyes.” Assigned corneas were from donors age 12 to 75 years (median age 61 years) with a central endothelial cell density (ECD) measured by each study eye bank at the time of screening of at least 2300 cells/mm². Surgeons either received the lenticule after eye bank–prepared lamellar dissection or had donor tissue shipped for surgeon preparation at the time of the DSAEK. For the eye bank–prepared donor lenticules, the eye bank prospectively noted whether the storage solution was exchanged with fresh solution before shipment to the surgeon (Fresh group) or the lenticule was returned to the original solution (Original group). Only 5 surgeons supported by 5 eye banks, performed their own lamellar dissection at the time of surgery with 343 (26%) of the donors stored in the original storage solution up until surgery. Data from these cases were not included in the comparisons of the Fresh and Original groups because these data are not relevant for addressing the current pressing clinical question facing eye banks to conserve storage solution and not exchange with fresh solution at the time of DSAEK or DMEK lenticule preparation.

Postoperatively, recipient stroma clarity was determined at 6, 12, 24, and 36 months or on interim visits if graft failure suspected. Graft failure was defined as cloudy initially with or without intraoperative/preoperative complications within 8 weeks postoperatively (early or primary, respectively) or after 8 weeks initially clear postoperatively then becoming cloudy because of rejection or nonrejection failure or refractive/visual failure.

**Donor Rim Cultures**

Donor corneal rim bacterial and fungal culture results were collected when performed by 43 of the 70 (61.4%)
surgeons at 26 of the 40 (65.0%) clinical sites as part of the surgeon’s routine and were not a protocol requirement.7 Donor corneas that were cultured were provided by 17 of the 23 (73.9%) eye banks in the CPTS. Sites provided data on the specimen type (donor rim tissue and/or storage solution), culture results (positive growth or no growth), and treatment initiated based on positive cultures. If only storage solution (without rims) was cultured, these data were not included. If growth was positive, for each specimen cultured, the name of each organism and the quantification of growth were obtained from the laboratory report. Cases of ocular infections were identified, and data were collected regarding characteristics of the adverse reactions.

Endothelial Imaging and Image Analysis
Details for central endothelial imaging and analysis have been previously published.6 The Cornea Image Analysis Reading Center (CIARC, Cleveland, OH) served as the central image analysis reading center to determine ECD and also was responsible for quality control measures at the eye banks and clinical sites. In summary, each eye bank obtained 1 to 3 specular image(s) of the central donor cornal endothelium on screening and determined ECD by their usual image analysis method. The eye bank also obtained 3 “preoperative” study images of the central endothelium either after lamellar dissection or, if the donor cornea was to be prepared by the surgeon, before shipment. Postoperatively, 3 images of the central endothelium were obtained at 6, 12, 24, and 36 months postoperatively.

Screening donor, preoperative, and postoperative images were evaluated for quality and ECD by the CIARC. Details of CIARC procedures have been previously described, including reader training and certification, image quality grading, image calibration, variable frame analysis for ECD determination, and adjudication procedures for image quality and ECD determination.6,8 The ECD of all analyzable images was independently determined by 2 readers using the variable frame analysis method where the reader counts cells within an outlined area of a group of cells, as in the Specular Microscopy Ancillary Study of the Cornea Donor Study.9

Statistical Methods
The statistical methods paralleled those used in the original CPTS analysis.2,6 Because the CPTS results indicated that the graft failure rate was not associated with PT through 11 days but was higher with PT >11 days, the analyses were restricted to the 791 cases with PT ≤11 days. Kaplan–Meier estimates of 3-year graft success and 95% confidence intervals (CIs) were computed separately for each storage type. The effect of storage type on 3-year graft failure was evaluated using univariate and multivariate Cox proportional hazards models. The supremum test was used to test the proportional hazards assumption and indicated no significant deviation from this assumption (P = 0.30). These models included a random participant effect to account for correlated data from study participants with 2 study corneas. The multivariate model adjusted for corneal diagnosis, donor age, donor PT, and donor pleomorphism/polymegethism. Hazard ratios, CIs, and P values are reported from the models. To assess the effect of storage solution on ECD, a linear mixed model was used adjusting for ECD at screening, corneal diagnosis, storage solution, and preparation by eye bank versus surgeon. Random participant and donor effects were adjusted for to account for correlated data from participants with 2 study eyes or 2 corneas from the same donor. The frequency of positive donor rim cultures in each group was compared using the Barnard exact test. All 95% CIs and P values are two-sided, and statistical significance was defined as P < 0.05 for all analyses. Statistical analyses were conducted using SAS version 9.4 (Cary, NC).

RESULTS
After lamellar dissection, the storage solution was exchanged for fresh solution for 508 donor corneas [Fresh group, 471 corneas (93%) OptiSol GS and 37 (7%) Life 4°C] and maintained in the original storage solution including its reuse after lamellar dissection for 283 eyes [Original group, 280 (99%) OptiSol GS and 3 (1%) Life 4°C]. Fifteen study eye banks exclusively used a fresh solution, 4 exclusively used an original solution, and 1 used both. Supplemental Digital Content 1 and 2 (see Table 1 and 2, http://links.lww.com/ICO/B430 and http://links.lww.com/ICO/B431) show the donor and recipient demographics for the 2 solution procedure groups, showing no major difference at baseline for any of these parameters.

The probability of graft success over the 3 years after surgery is shown in Figure 1. At 3 years after surgery, the Fresh group had a graft success rate of 93.4% (95% CI, 90.7%–95.3%), while the graft success rate in the Original group was 95.2% (95% CI, 91.8%–97.2%; Fig. 1). The unadjusted hazard ratio for 3-year graft failure in the Original group compared with the Fresh group was 0.71 (95% CI, 0.37–1.36; P = 0.30). After adjusting for corneal diagnosis, donor age, PT, and presence of donor pleomorphism/polymegethism, the hazard ratio for failure was 0.64 (95% CI, 0.33–1.24; P = 0.19; Table 1).

In the Fresh group, the mean ± SD ECD was 2752 ± 302 cells/mm² at screening and declined to 1520 ± 629 cells/mm² at the 3-year follow-up (mean ± SD ECL = 45% ± 22%). In the Original group, the mean ± SD ECD was 2677 ± 287 cells/mm² and declined to 1651 ± 546 cells/mm² at 3 years (mean ± SD ECL = 38% ± 20%). After adjusting for screening ECD, corneal diagnosis, storage solution, and preparation by eye bank versus surgeon, the mean difference in ECD between the Original and Fresh groups at 3 years was 157 cells/mm² (95% CI, 52–263; P = 0.004) favoring the Original group (Table 2).

Cultures were positive in 4 (1.5%) of 267 cultured donor rims (3 fungal and 1 bacterial) in the Fresh group and in 4 (2.5%) of 158 (2 fungal and 2 bacterial) in the Original group (P = 0.57) (subset of previously reported data from the CPTS).7 There were 2 postoperative infections in the Original group (previously reported Case 2 with Candida albicans keratitis and Case 3 with E. coli endophthalmitis)7 and none in the Fresh group.
DISCUSSION

Because the intermediate-term cold storage solutions at 2–8°C were introduced in the United States in the early 1990s, first OptiSol\(^1\) without streptomycin, then OptiSol GS\(^2\) with streptomycin, and then Life 4°C\(^3\) and Eusol-C\(^4\) eye banks have first used these FDA-approved solutions stored at 2–8°C for PKP for the entire storage period without exchange. However, with the emergence of EK for the management of endothelial failure conditions, initially with DSAEK and then DMEK,\(^5\) eye banks have progressively assumed the responsibility of lenticule preparation during the storage period and more recently loading the prepared lenticule into an injector system. In the development of their standard operating procedures, each eye bank has to make the decision whether to exchange the storage solution with fresh solution or to use the original solution and place the lenticule back into that solution. The adoption of either procedure was ultimately the eye bank’s medical director’s responsibility with no opinion expressed in the Eye Bank Association of America’s Medical Standards\(^6\) or Procedures Manual\(^7\) for which accreditation of that eye bank is based on. This solution exchange procedure was developed under the assumption that this exchange would help preserve the endothelium by removal of any toxic metabolites accumulated during the original storage period and manage any microbial contamination during the lenticule preparation and/or loading of the lenticule into the injector. However, there was and has been no evidence whether this exchange procedure has any short-term or long-term benefit for infection prevention and graft outcomes. Our secondary analyses from the prospectively gathered data from the CPTS suggest no major advantage for this fresh solution exchange in 3-year graft outcomes at least up to 11 days of storage, while the microbial contamination and prevention of infection question with fresh storage solution exchange is less definitive.

About endothelial health, all intermediate-term cold storage solutions achieved FDA approval as devices up to 2 weeks in storage at 2–8°C by means of endothelial viability studies for the entire storage period; however, the producing companies were not required to complete clinical trials to demonstrate efficacy and safety about graft outcomes.\(^8\)–\(^10\) No major multicenter\(^11\) or single-center clinical trials\(^12\)–\(^23\) for PKP or DSAEK graft outcomes (graft success and ECL) have commented in their methods regarding their storage solution procedures. Similarly, there has been no mention of the storage solution procedure for major DMEK graft outcome reports.\(^24\)–\(^30\) Thus, our study provides the first time long-term graft outcome evidence for graft success that support the endothelial viability that led to approval of these storage solutions for at least 11 days and at least for this reason that there is no need to exchange for a fresh solution to support endothelial viability. Interestingly, ECL for clear grafts at 3 years was greater in the Fresh group (45%) than the Original group (38%). We have no specific explanation for this difference, but the difference did not affect the graft success findings.

### TABLE 1. Effect of Storage Solution Procedure Type on 3-Year Graft Outcome*

| Storage solution procedure type | 3-year Graft Success Rate (95% CI) | Unadjusted Hazard Ratio for Graft Failure (95% CI) (\(P\)†) | Adjusted Hazard Ratio for Graft Failure (95% CI) (\(P\)‡) |
|-------------------------------|-----------------------------------|-------------------------------------------------|-------------------------------------------------|
| Fresh§                         | 508                               | 93.4%\(^*\) (90.7%, 95.3%)                      | 1.00 (1.00, 1.00)                               |
| Original†                      | 283                               | 95.2%\(^*\) (91.8%, 97.2%)                      | 0.71 (0.37, 1.36)                               |

*All models accounted for correlated data from study participants with 2 study corneas. Because no donor pairs had multiple failures, models did not adjust for random donor effect.

†Hazard ratios, confidence intervals, and \(P\) values are computed using a Cox proportional hazards model.

‡Adjusted for corneal diagnosis, donor age, donor preservation time, and donor pleomorphism/polymegethism.

§Storage solution exchanged with fresh solution after lamellar dissection.

††Original solution used throughout storage period including after lamellar dissection.

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FIGURE 1. Kaplan-Meier estimates of graft success during the 3-years post-surgery by storage solution procedure type (Fresh \(n = 508\)) and Original \(n = 283\)). The probability of graft success at 3 years post-surgery was 93.4% (90.7%, 95.3%) in the Fresh group and 95.2% (91.8%, 97.2%) in the Original group. The inset shows the same data on a truncated vertical axis.
Regarding the risk for contamination with the reuse of the original storage solution at the time of lenticule preparation and/or loading of the lenticule into the injector, our results are conflicting. Although our donor rim culture data showed no difference between the 2 storage solution procedures in positivity rates, both infections (one fungal and one bacterial) occurred in the Original group, with no infections in the Fresh group; unfortunately, donor rim cultures were not obtained on these 2 infection cases. However, our positive rim culture rate for both Fresh (1.5%) and Original (2.5%) groups as part of the larger CPTS cohort undergoing DSAEK7 was comparable with previous reports,31,32 and our microbial infection rate in the Original group (2 of 283 cases, 1%) and in the Fresh group (0 of 308 donors, 0%) was also comparable with previous reports.33,34 In addition, the mate of the reported fungal case (C. albicans) also developed a C. albicans infection in the recipient, suggesting that for this particular donor, the infections were tissue related and not related to the exchange or reuse of the original storage solution.3 However, at least based on the lack of a significant difference in the culture positivity rate and infection rate between the 2 groups, the use of the original storage solution throughout the storage period did not add risk for infection postoperatively. It should be noted that the incidence of positive rim cultures in our sample was low which limits our ability to evaluate the impact of storage solution on rim cultures.

Understandably, these findings are derived from secondary analyses and do not have the same weight of significance as the findings from a randomized clinical trial. Because standard procedures of all but one of the study eye banks were to uniformly use fresh solution or reuse the original solution, there could be selection bias if the original solution versus fresh solution eye bank’s preparation of the donor corneas for keratoplasty differed in ways, other than the use of fresh solution or reuse of the original solution, that were associated with the probability of graft success. Such a bias could be the explanation for why the ECL at 3 years was slightly lower in the Original group compared with the Fresh group. Notably, storage solution and the exchange of storage solution as eye bank variables did not emerge as significant factors influencing primary, early, or late graft failures and ECL using different statistical modeling techniques in the CPTS.22,23,35

In summary, in response to the current shortage of intermediate-term cold storage solutions in the United States and the need to conserve current and even future supplies of these solutions, we took the opportunity to examine the CPTS data to evaluate the influence of use of the original storage solution throughout the storage period compared with the exchange with fresh solution at the time of lenticule preparation on DSAEK graft outcomes. The continued use of the original storage solution did not reduce the 3-year graft success rate or increase ECL. The donor rim culture positivity rate for the 2 groups was statistically comparable, and infection rates were similar to what has been reported in the literature. Although DSAEK was the EK procedure in the CPTS, it is likely that these results apply to DMEK as well, although DMEK, while also an EK procedure, involves a different technique for lenticule preparation and differing injector systems.

These findings warrant eye banks to consider, at least during interim periods with limited supply of storage solution, the use of the original storage solution for their DSAEK and even DMEK procedures throughout the storage period. With experience, there could be consideration of incorporation in the future the use of the original storage solution throughout the storage period into their standard operating procedure, while closely monitoring any change in postoperative microbial infections.

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