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RESEARCH

Temporal Variability in the Number of Medically Eligible Corneas Released for Glycerol Preservation: the Global Sight Network Experience

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ABSTRACT

CONTEXT: The Global Sight Network (GSN) is a consortium of 31 United States eye banks that repurpose medically eligible corneas unsuitable for penetrating or endothelial keratoplasty for other surgeries by preservation in glycerol.

OBJECTIVE: Corneas received from partner eye banks from 2008-2011 were analyzed for demographics and timing of tissue release to GSN.

METHODS: Tissues were divided into 2 classes, those that were deemed unsuitable due to low endothelial cell density, stromal scar, or small central clear zone (Lower Quality) and those that could not be placed before the 14-day expiration of intermediate storage medium (Unable to Place).

RESULTS: Analysis for weekly variations in availability indicated that Lower-Quality tissues were released more consistently across days of the week than Unable-to-Place tissues, which were released more frequently on Mondays and Thursdays. Analysis for seasonal variations in availability indicated that Lower-Quality and Unable-to-Place tissues were modulated by different factors, beyond overall death rate.

CONCLUSIONS: This analysis of medically eligible corneas released for glycerol preservation has suggested that United States eye banks efficiently manage their tissue recovery rates in meeting domestic needs and revealed new opportunities for tissue placement. The results of the present study also point to new opportunities for tissue placement, including glaucoma therapy and even emergent needs for keratoplasties in international settings.

KEYWORDS: cornea transplantation, eye banks, glaucoma surgery, keratoplasty

Members of the Eye Bank Association of America (EBAA) distributed 59,271 corneas for transplant surgery in 2010.[1] As a result of the high quality and professionalism in eye banking, most of these procedures are performed on a scheduled basis, with minimal waiting times. In the course of obtaining these transplantable tissues, 9,471 additional tissues from medically eligible donors were determined unsuitable for transplantation because of tissue characteristics discernible on specular microscopy and slit lamp examination. Disqualifying findings include low endothelial cell density, stromal scar, or small central clear zone.[1] In an era in which United States healthcare costs are increasingly scrutinized due to aging of the overall population, it seems prudent to examine these tissues closely for factors underlying their recovery and to find ways to use them for other purposes consistent with the original consent for donation, i.e., for sight-preserving surgeries.

A 2008 initiative by GSN took the latter approach, by revisiting glycerol, a decades-old preservation medium, to preserve corneas in an anhydrous state without refrigeration for extended periods.[2] A glycerol-preserved cornea, lacking viable endothelium, is suitable for patch material in tectonic procedures for emergency repair and other purposes,[3,4] including covering glaucoma drainage devices.[5,6] Corneas that have been decellularized by various means can

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serve as allograft material for lamellar keratoplasties, as evidenced by clinical outcomes studies of lyophilized[7] and irradiated corneas.[8] A long shelf-life preservation method such as glycerol may be particularly useful in international settings in which corneas are in short supply and transportation systems are underdeveloped.[9]

The GSN is a service of the Alabama Eye Bank that was conceived as a consortium of eye banks that would pool medically eligible tissues that were recovered in intermediate storage medium and found to be unsuitable for optical keratoplasty. These tissues are released to GSN for transfer to glycerol and distribution either to surgical centers or back to the contributing eye bank for placement. Herein, we provide statistics describing tissues released to GSN in a 3.5-year period following its inception. These data provide a unique opportunity to explore the dynamics of an eye banking system through systematic analysis of its discards, a technique borrowed from archaeology. In particular, impressions about variability in the timing of receiving tissues were quantified.

METHODS

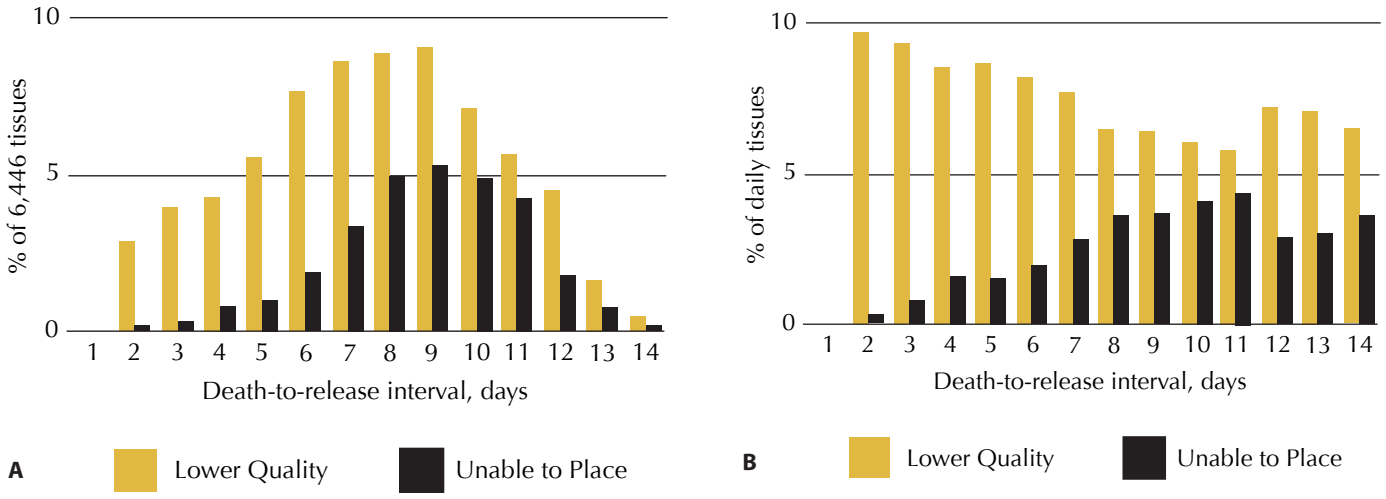
GSN, launched in November 2008, has grown to include 31 partner eye banks in 2 phases: a rapid phase in late 2008 and then a steady upward phase throughout 2010. This report covers 6,489 consecutive tissues processed between December 1, 2008, and June 30, 2011. Of these tissues, 5,403 (83.2%) were contributed by 14 large eye banks and 1,075 (16.7%) by 16 medium or small eye banks, with eye bank size specified in terms of the number of transplantable tissues as defined by the EBAA. These eye banks collectively handle more than 80% of transplantable corneas in the United States, indicating that the data are representative of the system as a whole.

All tissues processed by GSN are followed by a web-accessible tracking system using custom-built software (Filemaker) that conforms to the standards of the Food and Drug Administration and the EBAA. Partner eye banks indicate tissue availability by logging donor age, date, and time of death, as well as the results of their own serology tests and tissue assessments into a secure web-based portal. For this analysis, the time of release from partner eye banks to GSN (death-to-release interval) was considered equal to the time of tissue entry at the portal rather than the time of tissue arrival at GSN. Following removal of cases with missing or obviously incorrect data, 6,440 tissues constituted the dataset used for analysis (99.2% of the original dataset).

RESULTS

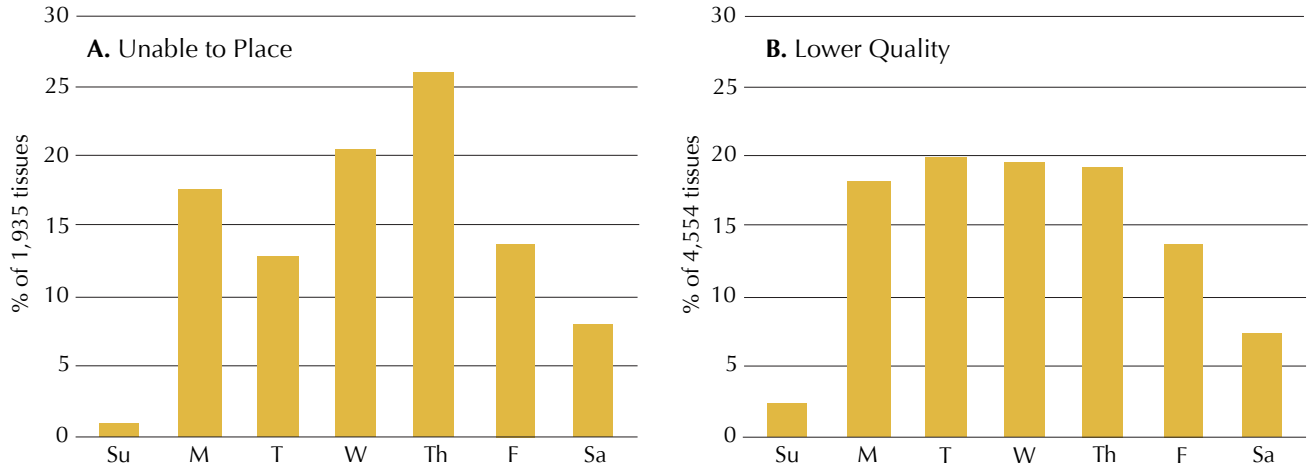
Medically eligible tissues were released by partner eye banks to GSN for 2 general reasons. The first

Fig. 1. Interval Between Donor Death and Time of Release to the Global Sight Network (GSN), 2008-2011



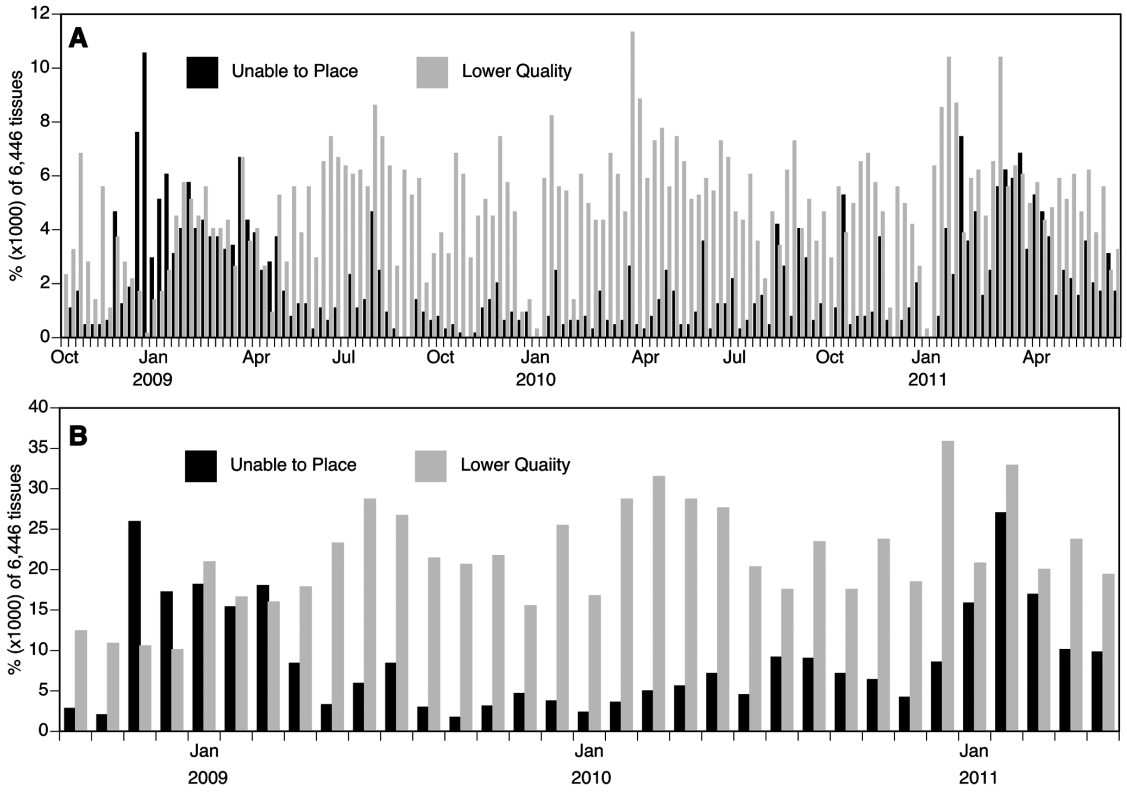
Tissues released to GSN are plotted as a function of days between death and release time for both Lower-Quality tissues and Unable-to-Place tissues: A, percentages of total tissues of each type; B, percentages of total tissues released each day after death. Lower Quality signifies that tissues had low endothelial cell counts, small central clear zones, or scarring. Unable to Place signifies that tissues were approaching the 14-day expiration date of the intermediate-term storage medium.

Fig. 2. Weekly Variation in the Number of Tissues Released to GSN, 2008-2011



reason was that the tissues did not meet endothelial cell density and other criteria for optical keratoplasties (n = 4,548, 70.6% of total; shown as "Lower Quality"). The other reason was that tissues suitable for optical keratoplasty were approaching the 14-day expiration of the intermediate storage medium and could not be placed for surgery (n = 1,892, 29.4% of total; shown as "Unable to Place"). Lower-Quality tissues arrived earlier in the medium expiration period than Unable-to-Place tissues (Fig. 1A). The proportion of

Fig. 3. Temporal Variation in the Number of Tissues Released to GSN



Data from October 2008 through June 2011 are shown: A, by week; B, by month.

Unable-to-Place tissues increased with the length of the death-to-release interval, from 10.7% at <4 days to 37.8% at 9-14 days (Fig. 1B). Of Unable-to-Place tissues, 42.0% (n = 806) were released within a death-to-release interval of 8 days.

The mean age of donors whose corneas were released to GSN was 62.6 ± 11.2 years (minimum 1 year, maximum 92 years), consistent with the age distribution of the overall cornea donor population (61.7 ± 18.7 years).[1] The ages of donors with Unable-to-Place tissues were significantly lower than those with Lower-Quality tissues (61.4 ± 12.05 years vs. 63.2 ± 10.7 years; P = 0.0000007, 2-tailed t-test for unequal variances).

Unable-to-Place tissues were compared to Lower-Quality tissues with respect to the timing of their release to GSN (Fig. 2 and 3). Fig. 2A shows the number of tissues released as a function of day of the week. Unable-to-Place tissues were released in a bolus on Mondays, followed by a drop-off on Tuesdays, and increased to a peak on Thursdays. In contrast, Fig. 2B shows that Lower-Quality tissues were released in similar numbers on Monday through Thursday, with decreased numbers released on Friday and Saturday.

These 2 tissue classes were analyzed as a function of the week of the year to reveal possible seasonal variations (Fig. 3A). The analysis included tissues from 4 calendar years, including 2 complete years (2009 and 2010). Several observations can be made. First, the number of Unable-to-Place tissues released per week was more variable than that of Lower-Quality tissues, as assessed by the coefficient of variation (standard deviation + mean; 95.3% vs. 42.3%, respectively). Second, in the first quarters of both 2009 and 2011, but not 2010, Unable-to-Place tissues were particularly numerous, comprising almost half of the total tissues released in many weeks. Third, the numbers of Unable-to-Place tissues were low and intermittent from June 2009 through the beginning of 2011, including several weeks of no tissues released. Fourth, the number of Unable-to-Place tissues spiked during the 2008 end-of-year holiday season (n = 49 and 68 on successive weeks), whereas in 2009 and 2010, few tissues of either type were received during that period. A maximum of 67-68 tissues per week were received in 4 weeks (1 each in December 2008, April 2010, February 2011, and March 2011).

To begin elucidating mechanisms that underlie temporal variation in tissues released to GSN, we reasoned that death rate should predict the overall availability of tissues for donation, if all aspects of the donation and recovery process were equally efficient. United States deaths due to all causes have been plotted as a function of month for the period 1968-2001 by Simonsen et al.[10] Their analysis shows a prominent cycle of increased deaths during every northern hemisphere winter (December-February) and decreased deaths in the summer, a yearly pattern typical of industrialized societies.[11,12] To facilitate comparison with this published dataset, Unable-to-Place and Lower-Quality tissues released to GSN were plotted by month (Fig. 3B). This analysis did not reveal such a cycle and peak for either tissue type.

DISCUSSION

We report descriptive statistics regarding tissues released to GSN for glycerol preservation during 2008-2011, with 3 main findings. First, tissues are contributed both for tissue quality and for non-distribution reasons. Second, tissues released to GSN exhibit distinct weekly and seasonal patterns. Third, more than 1,900 corneas released to GSN during the study period may have met criteria for penetrating and endothelial keratoplasties. These results have implications for eye bank services and for new tissue distribution opportunities.

Lower-Quality tissues constitute nearly 70% of those released to GSN. Even if the eye banking system were completely efficient at identifying medically eligible donors, corneas unsuitable for keratoplasty for tissue-based reasons will continue to be available and thus eligible for lamellar keratoplasty or non-keratoplasty use, at least in the near term. The continued availability of these tissues presents opportunities for investigating new biomaterial applications for which endothelial cell density, stromal scarring, or small central clear zones are not impediments. The opportunity most readily available to GSN was distribution of glycerol-preserved corneas for coverage of glaucoma drainage devices, as fresh and frozen corneas had been previously used for this purpose with good success.[5,6] Of tissues received by GSN during the study period, 38.1% have been placed for glaucoma shunt coverage, primarily to United States surgeons. Initial outcomes data for these placements are very promising with respect to low erosion rates relative to other coverage biomaterials (Wigton E, Swanner J, Joiner DW, et al. Outcomes of shunt tube coverage with glycerol preserved cornea versus pericardium. *Journal of Glaucoma* 2012, in press.) Most of the remaining GSN tissues are stored in anticipation of a continuously growing surgeon demand for this use.

We also found that approximately 30% of tissues released to GSN had an endothelial cell density >2000/mm^2 and a >7-mm clear zone but were not placed for penetrating or endothelial keratoplasties in the United States. The availability of tissues to a service such as GSN is a multifactorial process, including death rate; local cultural preferences about tissue donation; communication with families, hospitals, and organ procurement organizations; national holidays; shipping schedules; and other factors. Comparing the 2 tissue classes for timing of their release to GSN indicated that Lower-Quality and Unable-to-Place tissues are modulated by different factors on different time scales. The day-of-week analysis revealed that Unable-to-Place tissues were most frequently released on Thursdays. One scenario that could explain this finding is that following a donor death on a Tuesday, clearance of tissue for surgery after serological testing would occur too late in the workweek for surgeons who prefer to perform procedures early in the week. In contrast, Lower-Quality tissues are released throughout the week, with fewer on Friday and Saturday, likely in anticipation of GSN's weekend delivery policies. GSN's preferred courier service does not deliver on Sundays, and Saturday delivery is an option that GSN partners were asked not to exercise as of July 2010. Thus, tissues are not delivered on Saturday or Sunday, for 2 reasons, both of which affect the timing of tissues released to GSN before the weekend.

Lower-Quality tissues and Unable-to-Place tissues also have distinct seasons of availability to GSN. Both tissue types were released in an end-of-year holiday season surge in 2008, although few of either type were released during that period in subsequent years. It is possible that policies were instituted by partner eye banks between 2008 and 2009 to reduce overall recoveries in this season when both surgeons and patients are generally less available for elective surgery. An unusual finding was the increased number of Unable-to-Place tissues in early 2009 and 2011, but not in 2010. The basis of this year-to-year variation is unclear. It is interesting to note that there are no obvious peaks or troughs attributable to a system-wide hiatus created by the American Academy of Ophthalmology annual meeting in October. One factor that does not appear to be related to seasonal differences is the death rate. Deaths due to all-cause mortality are higher in the winter than in the summer in industrialized societies.[10,13] Variability in the timing of tissue release to GSN is not consistent with this pattern, suggesting that factors elsewhere in the recovery, referral, and distribution processes are influencing the numbers of tissues.

The existence of Unable-to-Place corneas is unusual in transplant medicine, and there are 2 ways to reduce the number of these optical keratoplasty-qualified tissues released to GSN: (1) control the number of recovered tissues and (2) identify more providers who can utilize them. With regard to recovery control, recent years have witnessed an outcomes-based approach to donor cornea retrieval—that is, identifying donor- and tissue-based factors that modify the likelihood of a successful corneal transplant. The Cornea Donor Study is a National Institutes of Health-funded investigation of the associations between donor-dependent factors such as age, endothelial cell counts, blood type, and surgical outcomes.[14-16] Early results showing that graft outcome 5 years after transplantation is not associated with donor age has been followed by a slow rise in the age of United States donors whose tissues are placed for transplantation, a phenomenon explained in part by the acceptance of these data and modification of surgeon preferences.[17] We anticipate that evolving tissue suitability criteria, surgeon preferences, and eye bank services in the wake of the Cornea Donor Study may eventually lower the number of tissues entering the Unable-to-Place category. With regard to additional providers, the fact that 42.0% of Unable-to-Place tissues were released to GSN ≤8 days after donor death means that as many as 800 tissues were received in sufficient time for shipping to some international providers. As a result of this analysis, GSN modified its practices to divert tissues from glycerol preservation to meet emergent needs for penetrating or endothelial keratoplasties in international settings (3.3% of tissues during study period). Many Unable-to-Place tissues had clear zones adequate for anterior lamellar keratoplasty, which does not require viable endothelium, raising the possibility that tissues could be diverted from glycerol for this purpose as well. GSN is continuing to pursue opportunities for distributing these tissues to other qualified international centers.

A strength of this study is its use of a highly representative sample of United States eye banks. A limitation is that the range of factors beyond death rates regulating release of medically eligible tissues was not fully identified. Future studies can investigate these factors in expanded datasets that include overall death rate, deaths referred to eye banks (in many cases through organ procurement organizations), total tissues recovered by eye banks, and eye bank policies and procedures.

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