Incidence of Acute Endophthalmitis Following Penetrating Keratoplasty

A Systematic Review

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Objective: To determine the incidence of acute endophthalmitis following penetrating keratoplasty (PK) over time.

Methods: A systematic review of English-language articles was conducted by performing a broad search of the PubMed database from 1963 through March 2003 using such keywords as penetrating keratoplasty, endophthalmitis, and postoperative complication. Additional studies were identified from bibliographies of relevant articles and published proceedings. The proportion of eyes with acute endophthalmitis as a postoperative complication was recorded, and pooled incidence rates were assessed over time.

Results: From 1870 unique, potentially relevant citations, 66 original studies that addressed endophthalmitis and met the selection criteria were analyzed. A total of 90,549 PKs were pooled, resulting in an overall estimate of 0.382% post-PK endophthalmitis, but a change over time was noted. The rate of endophthalmitis was 0.200% in the 2000-2003 period, 0.453% in the 1990s, 0.376% in the 1980s, and 0.142% during the 1970s. Furthermore, a downward trend in the incidence of endophthalmitis after 1992 was observed compared with 1991 and earlier.

Conclusions: This systematic review indicates that the incidence of endophthalmitis associated with PK has declined during the last decade.


ENDOPHTHALMITIS IS AN INFREQUENT BUT DEVASTATING INTRAOCULAR INFECTION WITH HIGH POTENTIAL FOR OCULAR MORBIDITY, INCLUDING PERMANENT SEVERE VISION LOSS.1 It has been classified by clinical setting and time of onset of clinically apparent inflammation into 4 categories: (1) postoperative (acute onset, delayed onset, bleb associated), (2) posttraumatic, (3) endogenous, and (4) miscellaneous (eg, secondary to microbial keratitis).1 Postoperative endophthalmitis is one of the most dreaded complications of intraocular surgery. The reported incidence of postoperative endophthalmitis varies by the specific surgical procedure and across studies, but the overall incidence has been declining since the late 19th century. Trends in the incidence of endophthalmitis following penetrating keratoplasty (PK), relative to cataract surgery, have been more difficult to follow owing to the smaller number of reported studies, but rates as high as 0.50% were reported until the late 1980s by a retrospective study based on nationwide patient registers.2

The relative rarity of endophthalmitis following intraocular surgery limits the ability of smaller studies to reveal clinical and statistical trends and demonstrates the difficulty in obtaining accurate incidence rates. Most reports regarding the rates of endophthalmitis are based on the experience of individual institutions or groups and are therefore limited by small sample sizes. Only more appropriate methods, such as comprehensive reviews or multicenter prospective studies, can help make comparisons and data statistically valid.

See also page 613

To obtain the best available perspective, as reflected by the medical literature, and a better understanding of the recent trends in postoperative endophthalmitis following PK, we conducted a systematic review of the literature. The purposes of this study were to detect changes in the trends of acute endophthalmitis following PK over time and to compare these with changes after cataract extraction.3 Changes in the incidence of this complication over time, if detected, might provide clues regarding the value of newer perioperative chemical disinfectants or more broad-spectrum antibiotics.

METHODS

STUDY DESIGN

We performed a systematic review of the literature to identify all published reports that per-
tained to the outcome of PK. The detailed methods used to identify, select, and analyze studies are described elsewhere. Briefly, studies were identified through (1) a computerized search of the Cochrane and PubMed (National Library of Medicine) databases from 1963 through March 2003, using a specific search strategy (Table 1); (2) a manual search of reference lists of original reports and review articles retrieved through the electronic search that met the selected criteria; (3) a review of major ophthalmic textbooks; and (4) a review of key published proceedings and scientific session abstracts (ie, Association for Research in Vision and Ophthalmology and American Academy of Ophthalmology). Keywords were selected based on expert opinion and evaluation of selected review articles on endophthalmitis and PK.

**SELECTION CRITERIA**

Reports were considered eligible for our review if they satisfied our selection criteria. Each article had to meet all of the following inclusion criteria: (1) the article was written in English, (2) the study examined human cases, (3) the study examined PK, and (4) the article addressed post–corneal transplantation endophthalmitis occurrence (ie, reported the number of procedures and the number of postsurgical endophthalmitis cases even if zero or the numbers could be derived according to reported percentages). Articles were excluded from this review if they met any of the following exclusion criteria: (1) the study examined fewer than 10 eyes, (2) endophthalmitis cases were associated with an outbreak (eg, contaminated instruments or media), or (3) the study had less than 1 week of postoperative follow-up (unless a relatively large number of endophthalmitis cases were identified, in which case the study was included).

**DATA ABSTRACTION**

Articles that satisfied the eligibility criteria underwent an intensive, structured review to abstract data on the postsurgical outcome of corneal transplant operations. Data extraction was performed using a standardized review form to record the following: (1) year of publication, (2) journal published, (3) location (ie, country) of trial, (4) the minimum (mean or maximum if minimum was not indicated) duration of follow-up on postsurgical patients, (5) number of eyes undergoing PK, and (6) number of patients who experienced acute endophthalmitis postoperatively (acute was defined as onset within 6 weeks).

**STATISTICAL ANALYSIS**

Details of the statistical methods used are described elsewhere. A weighted regression analysis was used to portray how the post-operative infection rates changed during the 40-year period from 1964 to 2003. The 40-year study period was also divided into 2 subperiods (ie, 1964-1991 and 1992-2003) to compare and contrast the trends with those of postcataract endophthalmitis occurrence. Infection rates were then fit by a weighted “piece-wise” or “segmented” linear model, composed of 2 separate linear approximations of the infection rates reported in the articles published within each subperiod. The weighted regression analyses were based on units of analysis as defined in 1 of the following ways: either the units of analysis were the 66 qualifying PK articles or they were the 40 years in which those publications appeared. In either case, the statistics were then weighted proportional to the number of surgical procedures reported within each unit of analysis, which gave more power to studies per year with a higher number of surgical procedures and less to those with fewer operations. All coefficients for this weighted regression model were computed using the SAS NLIN procedure (SAS Institute Inc, Cary, NC).

**RESULTS**

Figure 1 illustrates the flow of literature reviewed. Our computerized search identified 1723 unique citations, whereas a manual search of references resulted in 101 additional articles. From these, 66 studies fulfilled our eligibility criteria. The 66 studies were published in 1 textbook and 17 journals (Figure 2) and were categorized by the year of publication (Figure 3). The studies were published fairly evenly across years; the largest number of published studies in any single year was 6 in 1993. The highest number of PKs was also reported in 1993 (n=44 143), largely owing to a national database study.
of Medicare patients. There were no studies published in several years within the 1972-2002 period.

STUDY CHARACTERISTICS

The United States had by far the highest number of studies conducted (40), followed by Germany (3), India (3), the United Kingdom (3), African countries (2), Australia (2), Denmark (2), Israel (2), and Saudi Arabia (2). Canada, Finland, France, Singapore, Sweden, and Turkey each contributed 1 study to this analysis.

Figure 4 shows the distribution of sample sizes. The median number of corneal transplantations included in the 66 studies of our analysis was 159.5 (range, 10-40 351). The minimum (or mean if minimum was not indicated) duration of follow-up on postsurgical patients in the studies ranged from 1 month to 3 years.

OVERALL RESULTS

The overall pooled estimate (1972-2002) of the incidence of acute endophthalmitis after PK was 0.382% based on 90,549 PKs. The rate for each decade was: 0.142% in the 1970s, 0.376% in the 1980s, 0.453% in the 1990s, and 0.200% during 2000 and beyond (Figure 5). The rate of endophthalmitis from 1972 to 1999 was 0.392%, whereas the rate from 2000 to 2003 was 0.200%, repre-
senting an almost 2-fold decrease in the incidence (relative risk, 1.96; 95% confidence interval, 1.01-3.80).

**ENDOPHTHALMITIS FREQUENCY: TRENDS OVER TIME**

To assess and compare potential changes in the incidence of acute endophthalmitis following PK relative to cataract surgery during the last decade, we chose to compare the rates of post-PK endophthalmitis from before 1992 with those from 1992 forward. A weighted analysis of the mean endophthalmitis rate for each year or article was used, both producing the same results (Figure 6A and B). The slope obtained for the years 1972-1991 was +0.0174 (suggesting a gradual uptrend), whereas the slope from 1992-2003 (−0.0208) was consistent with a gradual decrease. The difference between these 2 slopes was statistically significant (Figure 7).

**CATARACT SURGERY VS PK**

Overall, the rate of acute endophthalmitis following PK (0.382%) was higher than that following cataract surgery (0.128%), representing an almost 3-fold increased risk associated with PK (Table 2). However, the trend for this risk has changed during the last decade, with PK demonstrating a gradual downtrend, in contrast to cataract surgery (Figure 7). The higher overall rate of endophthalmitis for keratoplasty compared with cataract extraction was statistically significant (P<.001), but the reverse was true after 2000, although the P value was not statistically significant (P = .40).

**COMMENT**

The findings of this literature synthesis demonstrate an apparent decrease in the incidence of postoperative endophthalmitis following PK during the last decade. Our analysis for trends of endophthalmitis over time (Figure 6) revealed that postsurgical endophthalmitis after PK was on the rise from the early 1970s until 1992, when a statistically significant reversal of this trend was demonstrable. The opposite trends over time were observed for cataract surgery. The year 1992 was chosen as the break-
THEORIES AND MECHANISMS

While the incidence of acute endophthalmitis was increasing after cataract extraction,² according to our data, the incidence after PK decreased. Several possible explanations exist for an apparent decreased incidence of this complication. The increasingly widespread use of povidone-iodine to disinfect the ocular surface at the time of postmortem harvesting of the donor tissue⁴ and intraoperatively could account for less bacterial contamination of donor tissue,⁵,⁶ as well as less risk of infection from organisms present on the recipient’s ocular surface.

The evolution of eye-banking techniques may be another important factor to consider in the down-trend of endophthalmitis cases after PK. The addition of antibiotics for gentamicin-resistant species in the corneal storage media (eg, streptomycin for Optisol-GS [Bausch & Lomb, Irvine, Calif]) may also contribute to the achievement of a more appropriate environment for corneal transplantation. In addition, the greater gram-positive coverage offered by topical fluoroquinolones, introduced in the early 1990s and widely used (but in an off-label indication) for surgical prophylaxis, might theoretically contribute to a reduced incidence of endophthalmitis, which is typically related to gram-positive organisms. The data that support the value of perioperative antibiotics for ophthalmic surgical prophylaxis are, however, inconclusive at this time.⁹

STUDY LIMITATIONS

There are potential limitations to the present literature synthesis, some inherent to systematic reviews in general and some particular to our review. These limitations have been described elsewhere.³ Often, the reports do not provide detail regarding exactly what perioperative measures were used for infectious prophylaxis (eg, povidone-iodine or antibiotics), how surgical technique and adjunctive therapy might have varied among patients and surgeons, and other potentially relevant surgical details. Given these limitations, using the statistical methods described herein (eg, regression analysis and the weighting method), we have minimized the potential drawbacks for our trends analysis. Nonetheless, even with limitations in mind, we believe that the present review has allowed us to address the rate of a relatively rare complication (ie, post-PK acute endophthalmitis) using existing data with increased statistical power.

CONCLUSIONS

First conducted in 1905, corneal transplantation is now the most common transplant procedure performed in the United States. The high potential of expansion for its use highlights the importance of minimizing its complication rates. With more than 33,000 PKs performed each year in the United States alone⁶ and an estimated 100,000 PKs performed worldwide,⁹ any increase in the incidence of post-PK complications can result in large absolute numbers of postoperative endophthalmitis cases.

<table>
<thead>
<tr>
<th>Period</th>
<th>Cataract*</th>
<th>PK</th>
<th>RR for Cataract vs PK (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1964-2003</td>
<td>0.128</td>
<td>0.382</td>
<td>0.34 (0.30-0.37)</td>
</tr>
<tr>
<td>1964-1999</td>
<td>0.109</td>
<td>0.392</td>
<td>0.28 (0.25-0.31)</td>
</tr>
<tr>
<td>2000-2003</td>
<td>0.265</td>
<td>0.200</td>
<td>1.33 (0.69-2.56)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; PK, penetrating keratoplasty; RR, relative risk.
*Data available elsewhere.³

The current rate of endophthalmitis after PK (0.200% from 2000 and later vs 0.382% in 1963-1999) equals, respectively, 130 and 380 cases secondary to a seemingly preventable but uncomplicated elaboration.

The results of the present synthesis of the literature will need to be confirmed in further studies. Bias inevitably results from the selection of cases included in studies submitted or accepted for publication and hence can potentially affect a systematic review.³ One approach to the elimination of such bias is to attempt the gathering of non-published data from the institutions at which the participating studies were conducted. This is, however, logistically difficult. An alternative solution is to test the hypothesis generated by the review in a large-scale prospective controlled trial with defined inclusion and exclusion criteria, such as surgical technique and prophylactic measures.

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REFERENCES