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<tr>
<td>Author(s)</td>
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National Survey on Bullous Keratopathy in Japan

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Purpose: To present the results of a national survey on bullous keratopathy (BK) in Japan.

Methods: A cross-sectional national survey was conducted for 963 eyes with BK seen between 1999 and 2001 by members of the Japan Cornea Society. Demographic characteristics, type of surgery, complications, and postoperative outcome were analyzed.

Results: BK accounted for 24.2% (963 eyes) of total keratoplasties performed during the period. Graft clarity was maintained in 77.4% of cases, and immunological rejection and elevated intraocular pressure was noted in 10.8% and 15.3%, respectively. Cataract surgery was the most common cause of BK (n=428, 44.4%), and phacoemulcification and aspiration (PEA) were performed in approximately 40% of cases. BK secondary to laser iridotomy (LI) was the second most common cause of BK (n=225, 23.4%). LI was performed as a prophylactic measure in approximately half of these cases. BK developed with a mean duration of 6.8 years following LI. Fuchs’ dystrophy was the cause of BK in 18 eyes (1.9%).

Conclusion: The causes of BK in Japan are considerably different to those in other western countries. LI-related BKs showed a remarkably high number, whereas Fuchs’ dystrophy was observed only rarely.

Key Words: Corneal transplantation; Bullous keratopathy; Laser iridotomy; Cataract extraction
Introduction

Bullous keratopathy (BK) is one of the leading causes for corneal transplantation in many countries. A recent report from a university hospital in Japan indicated that the rate of BK for performing corneal transplantation increased from 20.5% in 1987 to 26.0% in 1992. This increase appears to be related to the recent increase in the ophthalmic surgery performed. The number of cataract procedures has shown an approximately 200% increase over the last 10 years, giving rise to about 0.9 million cases being performed annually in Japan. It is interesting that the causative diseases for BK seem to be different between Japan and other geographical areas such as the United States and Europe. For example, we have few instances of Fuchs’ dystrophy in Japan, while this particular disease is one of the leading reasons for corneal transplantation in many other countries. In response to the increase in BK, The Japan Cornea Society formed the BK Study Group to conduct a national survey on the causes and surgical outcomes of BK. Here, we report the results of that survey. A comparison between the results of the present study and those of previous reports is also made.

Methods

The Japan Bullous Keratopathy Study Group sent a questionnaire to each member of the Japan Cornea Society. Members electing to participate in the study were required to fill in data on each BK patient treated between January 1999 and December 2001. Patients with a history of previous corneal transplantation were excluded from the study, as they have a different background and prognosis. The patients` data included demographic characteristics, causes of BK, preoperative conditions, associated disorders, types of surgery performed, and postoperative outcomes. The files were then returned to be analyzed in detail by the study group members. If any uncertainty existed, direct inquiries were made with the doctor concerned.

Statistical analysis

Statistical significance was determined using chi-square analysis.
with the Fisher exact test. The Student t-test was used to analyze the statistical significance of the incidence of the parameters investigated. P values of less than 0.05 were considered to be significant.

Results

We sent out 448 questionnaires, of which 86 were returned (19.2%). The targeted institutions consisted of 38 university hospitals, 19 general hospitals, and 29 private ophthalmic hospitals, each of them are listed in the appendices. A total of 3972 keratoplasties were performed in the facilities participating in the survey. This accounted for 51.1% of all the keratoplasties performed nationwide during this period (data from the Japan Eye Bank Association). Cases of BK were found in 963 instances, accounting for 24.2% of the total of 3972 keratoplasties (Table 1). They were found in 402 males (41.7%) and 561 females (58.3%) with a mean age of 68.8 ± 12.3 yr (range: 15-94 yr). Mean observation period was 96.4 weeks. The causes of BK are shown in Figure 1. The most common cause of BK was cataract surgery (pseudophakic or aphakic BK: PBK/ABK, n=428, 44.4%), followed by laser iridotomy (LI, n=225, 23.4%), glaucoma surgery other than LI (n=51, 5.3%), trauma (n=40, 4.2%), glaucoma (n=26, 2.7%), and vitrectomy (n=21, 2.2%). Details of the main causes are described in the following section.

Overall results

All but 18 eyes (945 eyes) had been subjected to some kind of surgical intervention. Simple penetrating keratoplasty (PKP) was performed on 498 eyes (51.7%), and PKP with extracapsular cataract extraction (ECCE) or phacoemulcification and aspiration (PEA), with or without intraocular lens (IOL) insertion, was performed on 443 eyes (46.0%). Other 2 eyes had amniotic membrane transplantation, and surgical procedure was not available in 2 eyes. At the final examination, 728 grafts (75.6%) were
found to be clear, 153 (15.9%) eyes showed endothelial decompensation, and 61 (6.3%) showed opaque grafts due to other reasons. The data on the remaining 21 eyes were not available for analysis. As postoperative complications, elevated intraocular pressure was observed in 149 eyes (15.5%), endothelial rejection in 104 eyes (10.8%), infection in 29 eyes (3.0%), and vitreoretinal disorders in 15 eyes (1.6%). Primary graft failure was noted in 2 eyes (0.21%).

**PBK/ABK**

There were 428 patients with BKs caused by cataract surgery. These consisted of 204 males and 224 females with a mean age of 71.7 ± 11.0 yr. Among the various methods of lens extraction used, PEA was the most common (n=169, 39.5%), followed by ECCE (n=94, 22.0%) and intracapsular cataract extraction (ICCE, n=72, 16.8%). Posterior chamber IOL was used most commonly (231 eyes, 54.0%), followed by anterior chamber IOL (64 eyes, 20.1%). Iris-clip IOL was used in only 9 eyes (2.1%). One hundred eyes (23.4%) were aphakic, and IOL status was not available in 10 eyes. Sixty-two eyes had some intraoperative complications such as posterior capsule rupture, with or without vitreous loss (47 eyes).

As surgical procedures, simple PKP was performed on 304 eyes (71.0%), and combined manipulation with IOLs, such as IOL insertion (50 eyes), IOL exchange (49 eyes), and IOL removal (15 eyes), was also performed. At the final examination, 331 grafts (77.3%) remained clear. As postoperative complications, immunological rejection developed in 47 eyes (10.9%). Glaucoma and infection were noted in 73 (16.9%) and 11 eyes (2.6%), respectively (Table 2).

**LI-related BK**

BKS secondary to LI were observed in 225 eyes, accounting for 23.4% of total BKs. They were found to be more common in females (184 eyes, 81.8%) than in males,
and the mean age was 71.7 ± 7.8 yr (range: 48-89 yr). Out of the 50 cases in which information on type of laser instrument used was provided, an argon laser accounted for the vast majority of procedures (48 eyes, 96.0%). Information on laser application was only available in 23 cases, and this showed a large degree of variation. In the 17 eyes where data on the number of laser shots used was given, 11 eyes received more than 300 shots. Interval between LI and development of BK ranged between 2 months to 20 yr, with a mean duration of 6.8 yr. Reasons for employing LI were specified in 137 cases. They included treatment of acute angle closure glaucoma (69 eyes, 50.4%), prophylactic treatment for narrow angle eyes (51 eyes, 37.2%), and contralateral eye of acute angle closure glaucoma (17 eyes, 12.4%). As surgery for BK, triple procedure (PKP, ECCE or PEA, and IOL insertion) was the most commonly performed procedure (195 eyes, 86.7%). Graft clarity was found to have been maintained in 183 eyes (81.3%) at final examination. Postkeratoplasty glaucoma was noted in 23 eyes (10.1%). Immunological rejection and infection were observed in 18 (8.0%) and 5 eyes (2.2%), respectively.

Other surgery-related BK

Glaucoma procedures other than LI were found to be the third most common cause of BK in this study (n=51, 5.3%). Trabeculectomy, with or without the use of anti-metabolites, was the most common type of surgery. Vitrectomy was consisted to be the cause of BK in 21 eyes (2.2%). Fifteen eyes had anterior-posterior radial keratotomy (Sato`s radial keratotomy). These patients consisted of 11 males and 4 females with a mean age of 66.5 years. They had either simple PKP (7 eyes) or combined PKP and cataract surgeries (9 eyes). Thirteen of the 18 eyes (72.2%) were found to have a clear graft at the final examination.

BK secondary to trauma and ocular diseases

Trauma accounted for the fourth most common cause of BK (40 eyes, 4.2%), with approximately half of them (21 eyes) associated with a perforating injury. Fuchs` dystrophy was noted in only 18 eyes (1.9%). These patients consisted of 3 males and 15 females with an age range of between 62 to 76 yr (mean: 69.1±9.5 yr). Seven and 10
eyes had simple PKP and PKP combined with cataract surgery, respectively. Thirteen grafts (77.6%) remained clear. Glaucoma without surgical intervention, which was typically associated with a history of angle closure glaucoma, was noted in 26 eyes (2.7%). Other diseases such as keratitis/ulcers, herpetic diseases, and iritis were considered to be causes for BKs in 41 eyes.

Comparison of causes of BK

Table 2 summarizes the demographic characteristics, surgical methods, complications, and graft clarity of each cause of BK. Although no significant difference was found in mean ages among the different causes, there was a female predominance in LI and Fuchs` dystrophy-related BK. The incidence of combined surgery, that is, PKP and cataract/IOL surgery, was common in LI-related BK. There was no significant difference in endothelial rejection, elevated intraocular pressure, or clear graft among the different causes.

Discussion

There have been a number of reports from around the world, including the United States, Europe, the Middle East, Africa, Australia and Asia, on the reasons for performing corneal transplantation.\textsuperscript{1-31} The present study is the first national survey regarding the reasons for and outcome of corneal transplantation in Japan. The number of hospitals that participated in this survey accounted for only approximately one-fifth of the total number of questionnaires, as many questionnaires were sent to corneal specialists who are not routinely performing keratoplasty. We know that most of the participating facilities had corneal specialists who actively performing keratoplasty. As a result, the number of cases analyzed in the present study corresponded to approximately one-half of all corneal transplants performed in Japan during the study period. Although there was a potential bias as these are the results of only approximately 50% of whole cases, we believe that the current study reflects national trends in corneal transplantation in Japan.

We found that BK was one of the leading reasons for corneal transplantation,
which is in good accordance with reports from other areas around the world.\textsuperscript{4, 6-11, 13, 15-17, 19-21, 23, 26, 30, 31} This popularity probably reflects an increase in the number of intraocular surgeries being performed, as the majority of BKs developed following surgical interventions. The increase in the amount of ophthalmic surgery being performed in Japan means we can anticipate a concomitant increase in the number of cases of BK.

Several noteworthy characteristics regarding the cause of BK were found in this study. PBK/ABK was the leading cause of BK, accounting for approximately half of the total number. They included 72 ABK cases and many of the patients undergone cataract surgery decades ago and developed late endothelial decompensation, or there were cases that were planned to have ECCE or PEA with IOL insertion but not completed due to intraoperative complications. The popularity of PBK/ABK as causes for BK is similar to the figures for other geographical areas such as the United States and Europe. It is noteworthy, however, that the BK related to the use of AC-IOLs was approximately 15\% of the cases of PBK in the present study, less than that in other reports.\textsuperscript{11, 16, 20, 21, 23} It has been reported that PBK associated with the use of closed-loop AC-IOL peaked around the early 1990s,\textsuperscript{18, 23} following the popularity of the lens in cataract surgery in the 1980s. We are fortunate that the introduction of closed-loop AC-IOLs was delayed in Japan compared to the United States, resulting in fewer cases of AC-IOL-related PBK. It should also be noted that PEA was the most common surgical procedure in our series. This reflects the recent predominance of PEA over ECCE and ICCE in Japan.\textsuperscript{33} In spite of the recent advancements in cataract surgery, more patients are being treated by training doctors. Therefore, it is likely that there will be more cases of PBK/ABK, suggesting that a new educational program on cataract surgery should be set up in this new era of surgical technology.

The other characteristic identified in the current survey was that there was a strikingly large number of LI-related BK. Although the disorder has been reported,\textsuperscript{34-39} no one noted such a large number. The difference in the rate of LI-related BK between Japan and other western countries is probably attributable to the difference in prevalence of angle-closure glaucoma. Angle closure glaucoma and narrow angle is much higher in the East Asian population than in the Western population.\textsuperscript{40, 41} As LI has
been reported to be a recommended treatment for affected and contralateral eyes of acute angle closure glaucoma,\cite{42} we have many more patients who have had LI than do western countries.

It should be noted that approximately half of the cases developed BK following prophylactic LI, although it is possible that some of them had unrecognized glaucoma attacks. It is intriguing that endothelial decompensation developed long after LI (mean; 6.8 years) in our series, which is in good accordance with the previous reports.\cite{36,38,39} While there have been reports indicating negligible effects on the corneal endothelium after LI,\cite{43,44} significant increases in endothelial size have also been reported.\cite{35} The mechanism of LI-related BK remained unclear. Various hypotheses have been proposed for this, including increases of temperature in the local aqueous humor,\cite{38} breakdown of the blood-aqueous barrier, high energy delivered during LI, and changes in the fluid dynamics of the aqueous humor.\cite{45}

The vast majority of cases of LI-related BK developed following argon laser LI, but not following YAG laser LI. Although not conclusive, the use of the YAG laser may be advisable for LI, especially for patients who are susceptible to endothelial damage such as those with guttae, diabetes mellitus, or a history of glaucoma attack.\cite{36,37,46} Bigar and Witmer reported corneal endothelial loss in acute angle closure patients that had no surgery, along with an association of corneal guttatae in these patients.\cite{34} No data was available in this study regarding the presence/absence of such risk factors. It is fortunate that the surgical prognosis of LI-related BK is favorable. Most of the cases had combined PKP and cataract surgery, and the graft clarity rate was somewhat better than that for PBK/ABK (Table 2).

Sato-type anterior-posterior radial keratotomy is a surgical method for correcting myopia, and was performed mainly in the 1950s.\cite{47} As the importance of the corneal endothelium for corneal transparency was not recognized at the time that this type of surgery was performed, there was a large number of late corneal decompensation developing. Although the number was relatively small in our series (15 eyes), it should be noted that BK still developed even more than 40 years after surgery.\cite{48}
The causes of non-surgery-related BK also differed between the present study and previous reports. In particular, Fuchs` dystrophy, which is one of the main causes of BK in the United States and Europe, was associated with relatively few cases in the current study. It has been reported that this disease is rare in Asian countries, including Japan.\textsuperscript{6, 10, 31, 49} Since the introduction of specular microscopy, the corneal guttatae have been observed relatively commonly in Japanese subjects. However, patients with Fuchs` dystrophy that need corneal transplantation are still uncommon in Japan.\textsuperscript{50}

The overall surgical outcomes were favorable in this study. Although the follow-up period was less than 2 years, approximately three quarters of grafts remained clear, which is similar to the figures found in previous reports. Endothelial rejection was observed in only 10.8\% of patients, which is relatively low compared to that in other reports. This may be attributable to the inclusion of cases that had a short follow-up period. We did not determine any exclusion criteria for insufficient follow-up as analysis for reasons of BK was the main purpose of the study.

To summarize, through this first national survey, we have found that BK is one of the main reasons for corneal transplantation in Japan. PBK/ABK is the leading cause of BK, and in many cases it developed following PEA with the use of posterior-chamber IOLs. Approximately one fourth of BKs were caused secondary to laser iridotomy, a strikingly high rate compared with that in western countries. Fuchs` dystrophy was found to occur much less commonly than in western countries.
References


41. Foster PJ, Johnson GJ. Glaucoma in China: how big is the problem? Br J


Appendix; Participating hospitals (in alphabetical order)

Aichi Medical University Hospital, Asai Ophthalmology Clinic, Baptist Eye Clinic, Dokkyo University School of Medicine Hospital, Ehime Prefectual Kitauwa Hospital, Ehime University Hospital, Fukuchiyama City Hospital, Fujita Eye Clinic, Fukuyama Eye Clinic, Hayashi Eye Hospital, Hino Municipal Hospital, Hiroshima City Asa Hospital, Hiroshima University Hospital, Ideta Eye Hospital, Ishikawa Prefectural Central Hospital, Iwasaki Eye Clinic, Iwate Medical University Hospital, Iwakiri Eye Clinic, Japan Labour Health & Welfare Organization Kansai Rosai Hospital, Jichi Medical School Omiya Medical Center, Jusendo General Hospital, Kagoshima University Hospital, Kaiya Eye Clinic, Kanagawa Clinic Refractive Surgery Center, Kanazawa Medical University Hospital, Kanazawa Red Cross Hospital, Kanazawa University Hospital, Kasumigaura Medical Center, Keio University Hospital, Kimura Eye & Int. Med. Hospital, Kinki University Hospital, Kozuka Eye Center, Kumagai Eye Clinic, Kumamoto University Hospital, Kumamoto City Hospital, Kurume University Hospital, Gunma University Hospital, Kyorin University Hospital, Kyoto Prefectural University of Medicine, LUMINE Hatano Eye Clinic, Miyata Eye Hospital, Morioka Municipal Hospital, Nagata Eye Clinic, Nakagawa Hospital, Namegata District General Hospital, Nerima General Hospital, Niigata University Medical & Dental Hospital, Nihon University, Nippon Medical School Hospital, Nishikasai Inouye Eye Hospital, Nishi Eye Hospital, Ohashi Eye Clinic, Osaka Kosei Nenkin Hospital, Osaka Medical College Hospital, Osaka University Hospital, Ou Eye Clinic, Ogawa Red Cross Hospital, Refractive Eye Clinic, Ryogoku Eye Clinic, Saitama Red Cross Hospital, Seino Ophthalmic Clinic, Sudo Ganka Shinryojo, Sugita Eye Hospital, Takagi Ophthalmic Hospital, Tane Memorial Eye Hospital, Teikyo University Hospital, The Cancer institute Hospital of JFCR, Tochigi National Hospital, Toho University, Tokai University Hospital, Tokushima University Hospital, Tokyo Dental College, Tokyo Medical and Dental University Hospital Faculty of Medicine, Tokyo Medical University Hospital, Tokyo Medical University Kasumigaura Hospital, Tokyo Women's Medical University Hospital, Tomita Eye Clinic, Tsukuba University Hospital,
University Hospital of Occupational and Environmental Health, University of the Ryukyu Hospital, University of Tokyo Hospital, University of Yamanashi Hospital, Yamaguchi University Hospital, Yamana eye hospital, Yokohama City University Hospital, Yamagata University Hospital
Table 1. Number of keratoplasties and bullous keratopathy

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<thead>
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<th>Year</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>Total</th>
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<tr>
<td>KPs in Japan</td>
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<td>2650</td>
<td>2642</td>
<td>7779</td>
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<td>KPs in participating hospitals</td>
<td>1254</td>
<td>1330</td>
<td>1388</td>
<td>3972</td>
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<tr>
<td>BKs in participating hospitals</td>
<td>283</td>
<td>296</td>
<td>384</td>
<td>963</td>
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<td>BK in KP (%)</td>
<td>22.6</td>
<td>22.6</td>
<td>27.7</td>
<td>24.2</td>
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KP = keratoplasty; BK = bullous keratopathy
Table 2. Demographic profiles, treatment methods, and postoperative outcomes by cause of BK

<table>
<thead>
<tr>
<th>Causes</th>
<th>N</th>
<th>Mean age</th>
<th>%Male</th>
<th>%Simple PKP</th>
<th>Rejection (%)</th>
<th>Elevated IOP (%)</th>
<th>Clarity (%)</th>
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<tr>
<td>Cataract surgery</td>
<td>428</td>
<td>71.7±11.0</td>
<td>47.7</td>
<td>70.3</td>
<td>10.9</td>
<td>16.9</td>
<td>79.3</td>
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<tr>
<td>LI</td>
<td>225</td>
<td>71.7±7.8</td>
<td>18.2</td>
<td>10.4</td>
<td>8.0</td>
<td>10.1</td>
<td>82.8</td>
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<tr>
<td>Glaucoma surgery</td>
<td>56</td>
<td>64.0±14.8</td>
<td>55.4</td>
<td>73.2</td>
<td>17.9</td>
<td>3.6</td>
<td>69.6</td>
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<tr>
<td>Trauma</td>
<td>55</td>
<td>52.9±16.9</td>
<td>61.8</td>
<td>67.9</td>
<td>16.4</td>
<td>21.8</td>
<td>78.8</td>
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<td>Fuchs`</td>
<td>18</td>
<td>69.1±9.5</td>
<td>16.7</td>
<td>41.2</td>
<td>5.6</td>
<td>5.6</td>
<td>77.6</td>
</tr>
<tr>
<td>Sato`s surgery</td>
<td>15</td>
<td>66.3±3.8</td>
<td>73.3</td>
<td>33.3</td>
<td>13.3</td>
<td>6.7</td>
<td>85.7</td>
</tr>
<tr>
<td>All</td>
<td>963</td>
<td>68.8±12.3</td>
<td>41.7</td>
<td>51.6</td>
<td>10.8</td>
<td>15.3</td>
<td>77.4</td>
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BK = bullous keratopathy; LI = laser iridotomy; PKP = penetrating keratoplasty; IOP = intraocular pressure
Figure 1

- other diseases: 41
- Sato’s RK: 15
- birth injury: 15
- Fuchs’: 18
- vitrectomy: 21
- glaucoma: 26
- trauma: 40
- glaucoma surgery: 51
- ABK/PBK: 428
- LI: 225
- others: 83
- other diseases: 41
Figure legend

Figure 1. Causes of BK