• Clinical Research •

Comparative outcomes of the pathogen in cultured Jones tubes used in lacrimal bypass surgery according to follow up periods

Bo Hyun Park, Hui Kyung Kim, Yeon Ji Jo, Jong Soo Lee

Department of Ophthalmology, Pusan National University School of Medicine & Medical Research Institute of Pusan National University Hospital, Pusan 49241, Republic of Korea
Correspondence to: Jong Soo Lee. Department of Ophthalmology, Pusan National University Hospital, 179, Gudeok-ro, Seo-gu, Busan 49241, Republic of Korea. jongsool@pusan.ac.kr
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Abstract

● **AIM:** To evaluate the pathogens in cultured Jones tubes used in lacrimal bypass surgery according to the postoperative periods and to obtain data for the prevention of infection of functional lacrimal stent invention.

● **METHODS:** Totally 71 patients (81 eyes) who underwent the removal of Jones tubes were enrolled in study. All the removed Jones tubes were cultured for bacterial and fungal identification and tested for bacterial antibiotic sensitivity. The results were analyzed according to the duration of the inserted Jones tube after lacrimal bypass surgery.

● **RESULTS:** Of the 81 eyes, bacteria were isolated from 69 eyes (85.2%) and fungi from 6 eyes (7.4%). Among 69 eyes, 40.6% showed *Staphylococcus aureus* (*S. aureus*), 11.6% were *Pseudomonas aeruginosa* (*P. aeruginosa*). Gram-positive bacteria were isolated more than Gram-negative bacteria, but Gram-negative bacteria showed a higher incidence in the Jones tube implanted for over 10y (P=0.035). The antibiotic sensitivity test showed that 46.4% of *S. aureus* were resistant to oxacillin. In terms of antibiotics commonly used in ocular clinical practice, vancomycin was sensitive to *S. aureus* and *Streptococcus pneumoniae* (*S. pneumoniae*), amikacin responded to *P. aeruginosa* and *Proteus mirabilis* (*P. mirabilis*). Trimethoprim/sulfamethoxazole (TMP/SMX) was all sensitive to *S. aureus, S. pneumoniae* and *P. mirabilis* except *P. aeruginosa.*

● **CONCLUSION:** *S. aureus* is the most commonly found organism in the Jones tube after lacrimal bypass surgery, and 46.4% of them are methicillin-resistant *S. aureus* (MRSA), sensitive to vancomycin. Especially, *P. mirabilis* responded with amikacin is dominantly detected in the Jones tubes implanted for more than 10y.

● **KEYWORDS:** Jones tube; lacrimal bypass surgery; *Pseudomonas aeruginosa*; *Proteus mirabilis*; *Staphylococcus aureus*

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INTRODUCTION

Conjunctivodacryocystorhinostomy (CDCR) or lacrimal bypass surgery originally described by Jones in 1962[1] is the standard treatment for canalicular obstruction. In practice, this surgical procedure is used in cases of less than 8 mm of residual canaliculi, congenital agenesis of the punctum or canaliculi, permanent paralysis of the lacrimal pump and lacrimal canalicular obstruction caused by trauma, tumor, systemic chemotherapy and radiation therapy[2-4].

Once lacrimal tubes are inserted, they can be retained lifelong in case of no complications. Complications associated with the lacrimal tube include extrusion, tube displacement, obstruction, infection, granuloma and strabismus[5-7]. These complications can eventually lead to tube removal, thus affecting the success rate of lacrimal surgery.

Since the tube used for lacrimal bypass surgery is exposed directly to the nasal cavity and conjunctiva, there is highly risk of infection or inflammation. Kreis *et al*[8] reported periorbital emphysema associated with Jones tube. Vaidya *et al*[9] reported a case of Jones tube infection by multiple microorganisms including *Corynebacterium kroppenstedtii*. Kim *et al*[10] reported on the successful treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infection associated with Jones tube.

Table 1 Demographics and clinical data of subjects enrolled in this study mean±SD

Characteristics	Group 1 (<1y)	Group 2 (1-<5y)	Group 3 (5-<10y)	Group 4 (≥10y)
No. of eyes	23	38	11	9
Age (y)	62.7±9.9	61.8±11.1	66.5±8.1	60.2±12.7
Sex, *n* (%)				
Male	9 (39.1)	16 (42.1)	6 (54.5)	0
Female	14 (60.9)	22 (57.9)	5 (45.5)	9 (100)
Mean time to tube removal (mo)	4.74±2.21	30.2±12.80	80.0±13.7	132.6±8.15

However, there are only a few reports on the pathogens isolated from lacrimal tubes used in lacrimal bypass surgery. Therefore, we evaluated the pathogens isolated from Jones tube by culture and antibiotic sensitivity test according to the postoperative durations. These results will be useful to prevent and control infection of the lacrimal tube. And it will be useful for invention of a functional lacrimal stent with releasing antibiotics drug.

SUBJECTS AND METHODS

Ethical Approval This retrospective observational analysis was performed in adherence with the Declaration of Helsinki and approved by Institutional Review Board (IRB No.2009-018-095). Our report is a retrospective study, so we did not obtain informed consent from subjects.

Patients Seventy-one patients (81 eyes) who underwent removal of the Jones tube associated with lacrimal bypass surgery from Nov. 2006 to Jan. 2020 were enrolled in this study. The indications for Jones tube removal were ocular discomfort, infection, inflammation, tube migration or malposition. The procedure of tube removal was performed under local anesthesia for outpatients or inside the operation room. The tube was immediately sent to the microbiology laboratory in a transport medium tube. Then the removed Jones tubes were cultured to identify the bacteria and fungi using sheep blood agar, MacConkey agar, Chocolate agar, Sabouraud dextrose agar and Sabouraud dextrose chloramphenicol agar respectively.

Antibiotic sensitivity test (vancomycin, penicillin, erythromycin, gentamicin, clindamycin, oxacillin, ampicillin, amikacin, ciprofloxacin, ceftazole, tobramycin, aztreonam, and piperacillin *etc.*) was also performed.

Surgical Technique Surgery was performed following a previously reported method[11]. In summary, the Bowman's probe was introduced through an incision on the caruncle and was advanced smoothly across the lacrimal bone into the anterior portion of the middle turbinate through the incised caruncle. Then, Bowman's probe #0 was pushed to penetrate the lacrimal bone between the lacrimal sac and nasal mucosa. Penetration size of the lacrimal bone was widened with a punctal dilator for insertion of the Jones tube, which was introduced over the probe into the nasal cavity and the probe was pulled out superiorly from the inserted tube. The bypass Jones tube was held stable with a prolene 8-0 or 9-0 (Ethicon; Somerville, NJ, USA) suture passed through a hole in the flange and attached to the adjacent edge of the caruncle. The size of the tube was measured by estimating the length of the Bowman's probe from the caruncle to the tip of the probe, located about 2 to 3 mm above the nasal mucosal surface.

Outcomes The results of the culture and antibiotic sensitivity test were compared according to the duration of tube removal after surgery: Group 1: within 1y, Group 2: from 1 to less than 5y, Group 3: from 5 to less than 10y, Group 4: over 10y. Fisher's exact test was used for the comparison of parameters. A P-value ≤0.05 was considered statistically significant.

Morphological Findings The bacteria cultured from removed Jones tube were inoculated in the liquid medium, 2.5% lysogeny broth (Becton Dickinson and Company, Sparks MD, USA) and shaking incubated overnight at 37℃. Then incubated bacteria sample was fixed 1:1 with 1% glutaraldehyde (JUNSEI, Tokyo, Japan) for 30min. A fixed sample of 6 μL was pipetted onto a 100 mesh copper grid with carbon-coated formvar film (EMS, Hartfield, USA) and incubated for 10min. Excess liquid was removed by blotting. The grid was washed twice by brief contact with 100 μL distilled water, followed by blotting to remove excess liquid. Next, the grid was placed on 30 μL of 1% uranyl acetate (SPI, Westchester, USA) for 12s. After removing excess liquid by blotting, the sample was examined with a transmission electron microscope (JEM-1200EX II, JEOL, Tokyo, Japan).

RESULTS

Seventy-one patients (81 eyes) were included in this study. The mean age was 62.5±10.7y (range, 24-81y). There were 47 female patients (66.2%). The mean Jones tube removal period was 41.1±41.0mo (range, 1-153mo) after surgery. Of the 81 eyes studied, Jones tube was removed in 23 eyes within 1y, in 38 eyes 1y or more but less than 5y, in 11 eyes 5y or more but less than 10y, and in 9 eyes 10y or more than 10y (Table 1). The causes of Jones tube removal were patient's discomfort, infection or inflammation and tube malposition including migration. The tube was removed in 17 eyes (21.0%) due to

Table 2 Causes of Jones tube removal

Group	Eyes that underwent Jones tube removal, *n* (%)		
	Ocular discomfort	Inflammation or infection	Tube malposition or migration
Group 1 (<1y)	10 (43.5)	7 (30.4)	6 (26.1)
Group 2 (1-<5y)	6 (15.8)	9 (23.7)	23 (60.5)
Group 3 (5-<10y)	1 (9.1)	0	10 (90.9)
Group 4 (≥10y)	0	4 (44.4)	5 (55.6)
Total	17 (21.0)	20 (24.7)	44 (54.3)

Table 3 Cultured organisms found in Jones tubes after lacrimal bypass surgery according to the duration of tube removal

Type of cultured bacteria	Duration of tube removal after surgery			
	Group 1 (<1y)	Group 2 (1-<5y)	Group 3 (5-<10y)	Group 4 (≥10y)
Gram-positive bacteria				
S. aureus	5	16	5	2
Corynebacterium, C. species, C. macginleyi, C. pseudodiphtheriticum	4	4	0	0
S. pneumoniae	3	1	1	0
Gram-positive bacilli	3	2	0	0
Staphylococcus epidermidis	1	0	0	0
Staphylococcus constellatus	0	0	1	0
Staphylococcus caprae	0	1	0	0
Gram-negative bacteria				
P. aeruginosa	1	5	1	1
Serratia marcescens	1	2	0	0
Stenotrophomonas maltophilia	0	3	0	0
P. mirabilis	0	0	0	2
Sphingomonas paucimobilis	0	0	0	1
Enterobacter aerogenes	0	0	1	0
Citrobacter koseri	0	0	1	0
Acinetobacter nosocomialis	0	0	0	1
Total	18	34	10	7

S. aureus: Staphylococcus aureus; C. species: *Corynebacterium species*; *C. macginleyi*: *Corynebacterium macginleyi*; *C. pseudodiphtheriticum*: *Corynebacterium pseudodiphtheriticum; S. pneumoniae: Streptococcus pneumoniae; P. aeruginosa: Pseudomonas aeruginosa*; *P. mirabilis: Proteus mirabilis*.

ocular discomfort such as pain, foreign body sensation, and itching; in 20 eyes (24.7%) due to infection or inflammation, and in 44 eyes (54.3%) due to tube migration or malposition (Table 2).

Among the 81 eyes, bacteria were isolated from 69 eyes (85.2%). Gram-positive bacteria in 49 eyes (71.0%) and Gram-negative bacteria in 20 eyes (29.0%). Among the cultured bacteria, *Staphylococcus aureus* (*S. aureus*) was the most common bacterium (28 eyes, 40.6%) followed by *Pseudomonas aeruginosa* (*P. aeruginosa*, 8 eyes 11.6%).

Table 3 shows the culture pattern according to the duration of tube removal. When comparing each group divided by the implanted period, Gram-positive bacteria were found more often than Gram-negative bacteria in the group within 10y of lacrimal bypass surgery with *S. aureus* being the most common bacterium. However, more than 10y after the surgery, Gram-negative bacteria were more significantly found than Gram-positive bacteria comparing the whole group frequency (Fisher's exact test, P=0.035). And *Proteus mirabilis* (*P. mirabilis*) was the most common bacterium in the same number as *S. aureus* in Jones tube removed 10y after surgery (Figure 1).

In addition, 6 (7.40%) of the 81 eyes showed fungi such as *Tricosporon inkin* (1 eye), *Alternaria* (1 eye), *Aspergillus flavius* (1 eye) and *Candida parasilosis* (3 eyes).

The antibiotic sensitivity test showed that 89.3% of *S. aureus* had penicillin resistance and 46.4% of *S. aureus* were MRSA. *S. aureus* was sensitive to trimethoprim/sulfamethoxazole (TMP/SMX) and vancomycin, whereas piperacillin, amikacin, and gentamicin in *P. aeruginosa*. All of *P. mirabilis* in the Jones tubes implanted for more than 10y was sensitive to gentamicin, TMP/SMX, amikacin, and imipenem. Overall, vancomycin is sensitive to *S. aureus* and *Streptococcus pneumoniae* (*S. pneumoniae*), compared with *P. aeruginosa* and *P. mirabilis*

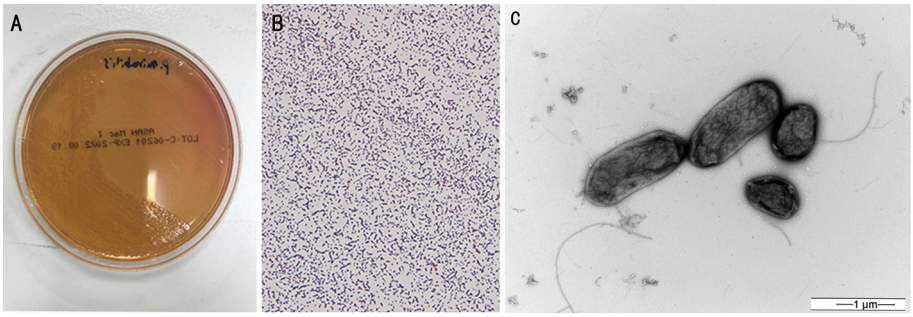

Figure 1 Morphological findings of *P. mirabilis* pathogens cultured in a Jones tube removed Colonial morphology, cell morphology and transmission electron microscophic morphology of *P. mirabilis. P. mirabilis* was cultured in removed Jones tube. A: The colonical morphology of *P. mirabilis* cultured in Macconkey agar medium. In this medium, the bacteria forms distinctive colonies different from the swarming colonies found in blood agar. B: The appearance of *P. mirabilis* after Gram staining with an optical microscope. *P. mirabilis* is gram negative bacterium. A pale reddish stained bacteria was distributed in pairs in optical microscope image (×400). C: The appearance of *P. mirabilis* using a transmission electron microscope. The bacteria showed a rod shape and had a few peritricheous flagella (Swimmer cell type). The average length of the bacteria was 1.5 μm (negative stain, original bar length: 1 μm, ×20 000). *P. mirabilis*: *Proteus mirabilis*.

Table 4 Antibiotic sensitivity test of cultured organism from Jones tubes

Antibiotics	No. of bacterium sensitive to antibiotics (%)			
	S. aureus (*n*=28)	*P. aeruginosa* (*n*=8)	*S. pneumoniae* (*n*=5)	*P. mirabilis* (*n*=2)
Penicillin	3 (10.7)	0	5 (100)	0
Oxacillin	15 (53.6)	0	0	0
Ciprofloxacin	15 (53.6)	7 (87.5)	0	1 (50)
Ceftazidime	0	8 (100)	0	1 (50)
Ceftriaxone	0	0	5 (100)	1 (50)
Clindamycin	16 (57.1)	0	2 (40)	0
Erythromycin	13 (46.4)	0	2 (40)	0
Gentamicin	18 (64.3)	8 (100)	0	2 (100)
Rifampin	26 (92.9)	0	0	0
TMP/SMX	28 (100)	0	5 (100)	2 (100)
Vancomycin	28 (100)	0	5 (100)	0
Levofloxacin	0	2 (25)	5 (100)	1 (50)
Amikacin	0	8 (100)	0	2 (100)
Imipenem	0	4 (50)	0	2 (100)
Piperacillin	0	8 (100)	0	1 (50)
Piperacillin/tazobactam	0	6 (75)	0	1 (50)
Tetracyclin	20 (71.4)	0	2 (40)	0

S. aureus: *Staphylococcus aureus*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *S. pneumoniae*: *Streptococcus pneumoniae*; *P. mirabilis*: *Proteus mirabilis*; TMP/SMX: Trimethoprim/sulfamethoxazole.

responded to amikacin. TMP/SMX showed sensitivity to *S. aureus, S. pneumoniae*, and *P. mirabilis* (Table 4).

DISCUSSION

The CDCR or lacrimal bypass surgery are used for treating disturbing epiphora due to a permanent failure of the canaliculi requiring a new passage for bypassing the lacrimal canaliculi and sac. Since its first description by Jones[1], it has been an acceptable and effective surgical technique with a high rate of surgical success. However, there are various complications of lacrimal surgery caused by the tube such as extrusion, malposition, obstruction, infection, and discomfort[12]. Among the complications, extrusion (5%-51%) and malposition (6%-33%) are the most common[13]. This is consistent with the result of our study that the most common cause of tube removal is associated with the location of the tube (54.3%).

Inflammation including infection occurs approximately 10% in lacrimal bypass surgery showing a lower incidence compared with complications related to the location of the tube[12-13]. However, it can lead to chronic inflammation of the conjunctiva, cornea, and lacrimal sac as well as serious complications such as endophthalmitis[14-16]. Thus, it is important to investigate the pathogenic strains and their antibiotic sensitivity for prevention and treatment of inflammation related with an implanted Jones tube. We

previously investigated the pathogens in cultured Jones tube and their antibiotic sensitivities for a few years, but there was some limitation of size of study and long term follow up period[11,17]. Thus, we collected a larger number of cases compared to the previous study and then analyzed the microbiological spectrum and antibiotic sensitivity profile of extubated Jones tube following lacrimal bypass surgery.

Among the 81 eyes that we studied, bacteria were found in 69 cases (85.2%), fungi in 6 cases (7.40%) and no organism in 6 cases (7.40%). Similar to a previous study[11], gram-positive bacteria were more frequently found than gram-negative bacteria within 10y of lacrimal bypass surgery. However, after 10y, Gram-negative bacteria were more common than gram-positive bacteria. It was statistically significant (Fisher exact test, P=0.035).

S. aureus, an independent pathogen, was the most common bacterium found in 28 eyes (40.6%). This result was consistent with that of previous studies[10,13,17]. Kim *et al*[10] reported that all patients suffered from tube infection were diagnosed with MRSA infection. Lim *et al*[13] reported that all of the infection of Jones tube were caused by *S. aureus.*

But, there is a difference from our previous study. In previous study, *P. mirabilis* was isolated most frequently after 10y of lacrimal bypass surgery[11]. But in this study, *S. aureus* and *P. mirabilis* was isolated in the same number after 10y of lacrimal bypass surgery. So, *S. aureus* was the most common bacteria in all periods in present study. Thus, if a person who underwent lacrimal bypass surgery shows signs of tube associated inflammation, regardless of the tube removal period, *S. aureus* should be considered as the primary pathogen for treatment. According to the antibiotic sensitive test, 89.3% of *S. aureus* were resistant to penicillin and 46.4% of *S. aureus* to oxacillin (MRSA). So, vancomycin is an effective antibiotic for tube associated infection. However, in patients who have undergone lacrimal bypass surgery over 10 years ago, if vancomycin treatment is ineffective, the possibility of Gram negative bacteria including *P. mirabilis* infection should be considered.

P. aeruginosa was the second most common bacterium found in 8 eyes (11.6%). And most of the gram-negative bacteria was *P. aeruginosa*. In the antibiotic sensitivity test, *P. aeruginosa* was found to be susceptible to gentamicin, amikacin, ceftazidime and piperacillin. So, based on our study results, aminoglycoside antibiotics (gentamicin or amikacin), ceftazidime and piperacillin may be recommended as the second-line therapy. *S. pneumoniae*, which was identified in 5 eyes (7.25%) in this study, was the third most common bacteria. They were sensitive to TMP/SMX, vancomycin, levofloxacin and ceftriaxone. So, considering the antibiotics commonly used in ophthalmology, vancomycin is sensitive to *S. aureus* and *S. pneumonia*, compared with *P. aeruginosa* and *P. mirabilis* responded to amikacin.

Recently, normal microbiota of eye and nose have been studied by using sequencing technology based on 16s rRNA. The most prevalent phyla in ocular surface are *Actinobacteria*, *Proteobacteria*, and *Firmicutus.* And, at the genus level, *Corynebacterium*, *Pseudomonas*, *Staphylococcus*, *Streptococcus*, *Acinetobacter*, *Propionibacterium*, *Agrobacterium*, *Sphinogomonas*, *Cutibacterium* and *Enhydrobacter* are found in normal ocular surface[18-19].

And, at genus and species level, the normal nasal microbiota include *Streptococcus* (*S. pneumoniae, Streptococcus mitis*), *Staphylococcus* (*Staphylococcus saccharolyticus*, *Staphylococcus epidermidis, Staphylococcus capitis, S. aureus*), *Moraxella* (*Moraxella catarrhalis*) and *Haemophilus* (*Haemophilus influenza*)[20]. We found that normal ocular and nasal flora such as *Corynebacterium*, *Staphylococci*, *Streptococcus, Acinetobacter, Sphinogomonas* were identified in our culture test. And our culture test results showed a similar pattern of bacterial identification in other study[21].

Bacterial biofilms are serious global health concern due to their abilities to tolerate antibiotics, host-defence systems and other external stresses[22]. Therefore, an increasing number of diseases including ocular infection have been suggested to be biofilm related[23-24]. As other medical devices, Jones tube and lacrimal stent may provide with a surface for biofilm formation[24-27]. Parsa *et al*[25] demonstrated the presence of bacterial biofilms in culture-negative Jones tube as a cause of chronic infection. Balikoglu-Yilmaz *et al*[26] reported that 90% of lacrimal stent removed 8wk after dacryocystorhinostomy revealed the presence of biofilm with cocci and/or rod shape bacteria. Kim *et al*[27] succeeded in making a biofilm on the lacrimal stent with *S. aureus* and *P. aerugionosa.* Although there is a question whether the presence of biofilm is the cause of the infection, it is important to find out the pathogen to from biofilm and their antibiotic sensitivity due to its difficulty of treating biofilm related infection[22,28]. Since some of the bacteria found in our study can form biofilm[27], our study results may help preventing biofilm related infection.

Normal ocular surface include 65 different fungal genera including *Aspergillus*, *Setosphaeria*, *Malassezia*, *Haematonectria*, *Candida etc*[28]. In our study, six eyes (7.40%) were found in fungus, *Candida parasilosis* (3 eyes), *Aspergillus flavius* (1 eye), *Tricosporon inkin* (1 eye), and *Alternaria* (1 eye). So if various antibiotics do not respond to treatment, it is necessary to consider infection caused by fungi, especially *Candida* species. In this case, first of all, topical eye drops such as amphotericin B 0.15%, natamycin 5%, voriconazole 1% and systemic administration of antifungal

drug series like azoles are recommended[29].

In conclusion, this study identified various strains in the culture of Jones tube after lacrimal bypass surgery and their antibiotic sensitivity. *S. aureus*, *P. aeruginosa*, *S. pneumoniae, P. mirabilis* can lead to Jones tube related infection. And 46.4% of *S. aureus* were MRSA. For antibiotics commonly used in ophthalmology, vancomycin is sensitive to *S. aureus* and *S. pneumoniae*, compared with *P. aeruginosa* and *P. mirabilis* responded to amikacin. TMP/SMX showed sensitivity to *S. aureus, S. pneumoniae* and *P. mirabilis.* The results of this study will help prevent lacrimal tube related infection and use antibiotics properly. Furthermore, our study will serve a potential role in the development of special functional lacrimal tubes such as the biofilm inhibitory or antibiotic drug-releasing lacrimal tubes.

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CORRIGENDUM

Nintedanib induces apoptosis in human pterygium cells through the FGFR2-ERK signalling pathway

Yan Gong, Yan-Hong Liao, Quan-Yong Yi, Meng Li, Li-Shuang Chen, Yan-Yan Wang
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