Research Protocol

Title of manuscript: Endoscopic Dacryocystorhinostomy as Primary versus Secondary Treatment in Acute Dacryocystitis: A randomized controlled trial

Background:

Acute dacryocystitis refers to acute inflammation of the lacrimal sac, commonly associated with abscess formation. It is usually a secondary bacterial infection in the presence of nasolacrimal duct obstruction (NLDO) of various origins [1, 2]. Conventional treatment for acute dacryocystitis with abscess formation consists of warm compresses, systemic antibiotics and percutaneous abscess drainage, followed by external dacryocystorhinostomy (DCR) when acute infection has subsided [3]. This treatment strategy, however, has several limitations. Since the underlying pathology of NLDO is not corrected in the initial stage, there may be prolonged or recurrent infection. Percutaneous abscess drainage may result in unsightly cutaneous scar and fistula formation. The resultant fibrous scar and granulation tissue in the lacrimal drainage system may increase the failure of subsequent lacrimal system reconstruction. Surgical intervention in two-stage also increases patients’ discomfort and duration of hospital stay.

Over the past decade, a few authors have reported their positive experience of endoscopic dacryocystorhinostomy (EN-DCR) as the primary treatment in acute dacryocystitis [4-8]. The main advantage of EN-DCR in the initial stage is that it provides adequate and continuous drainage of the lacrimal abscess which lead to rapid resolution of inflammation, and by correcting the causative pathology of NLDO, the chance of recurrence is reduced. Other advantages include simultaneous correction of concurrent nasal pathology, lack of cutaneous scar, shorter overall recovery time, reduced hospital stay and lower cost. However, most of the studies on this topic are retrospective case series and the efficacies of EN-DCR in the setting of acute inflammation vary widely. The long-term ostial patency ranged from 67% to 94% [4-8]. Wu at el performed the first prospective randomized trial comparing primary endonasal EN-DCR and secondary external DCR and showed the former was significantly better in terms of acute pain relief and ostial patency at 12 months [7]. Despite a well designed study, it might not be appropriate to directly compare the ostial patency rate of two different ways of performing DCR. Moreover, in our population, EN-DCR is preferred over external DCR, either as primary or secondary procedure, as unsightly scar with post-inflammatory hyperpigmentation is frequently an issue. We are, therefore, more interested to know whether performing EN-DCR in the setting of acute inflammation jeopardize the efficacy of the procedure in correcting the underlying NLDO. The aim of this study is to compare the clinical outcomes of EN-DCR as primary treatment and as secondary treatment in acute dacryocystitis.
Objectives:
To compare the clinical outcomes of endoscopic dacryocystorhinostomy (EN-DCR) as primary treatment and as secondary treatment after inflammation subsided with initial percutaneous drainage of lacrimal abscess in acute dacryocystitis

Hypothesis:
EN-DCR as primary treatment of acute dacryocystitis is a non-inferior option compared to conventional management strategy

Methods:
*Trial design*
Randomized controlled trial in the allocation ratio of 1:1

*Participants*
Inclusion criteria:
- Subjects with acute dacryocystitis, defined as painful lacrimal sac distention with marked medial canthal inflammation of less than 2 weeks
- Age 18-90
- Fit for operation under general anesthesia

Exclusion criteria:
- History of DCR
- History of trauma / neoplasm / congenital anomalies of lacrimal drainage system
- History maxillofacial surgery or trauma
- Immunocompromized patients
- Poor cooperation for operation or subsequent endoscopic examination
- Fail or refuse to give consent

Setting and location for participants recruitment
- Outpatient clinics and inpatient consultation in Hong Kong Eye Hospital, Queen Elizabeth Hospital and Prince of Wales Hospital with diagnosis if acute dacryocystitis confirmed by oculoplastic surgeons in the corresponding institution.
Sample size calculation

Non-inferiority test

N = 32, control group (n₁) = 16, intervention group (n₂) = 16

Formula

\[ n₁ = \left( z_α + z_β \right)^2 \left[ \frac{rθ₁(1-θ₁) + θ₂(1-θ₂)}{(θ₁-θ₂-δ)^2} \right] \]

\[ n₂ = rn₁ \]

Notations:

\( \alpha \) = the probability of type I error = 0.05
\( \beta \) = the probability of type II error = 0.2
\( θ₁ \) = expected success rate of intervention group = 0.7
\( θ₂ \) = expected success rate of control group = 0.96
\( r \) = allocation ratio, i.e. \( n₂/n₁ \), = 1, for equal allocation.
\( δ < 0 \) for non-inferiority

Interventions

Control group:

Patient will be offered percutaneous lacrimal abscess drainage under local anesthesia on the same day of presentation after randomization. A course of empirical systemic antibiotics will be given. The drainage site will be laid open, followed by regular dressing of the wound until infection subsided. Repeated percutaneous drainage of lacrimal abscess is allowed in case infection fails to resolve. EN-DCR will be performed within 1 month after acute dacryocystitis subsides as a secondary treatment of the underlying nasolacrimal duct obstruction.

Treatment group:

Patient will be offered EN-DCR as a primary treatment for acute dacryocystitis within 2 weeks after presentation and randomization. Empirical systemic antibiotics will be giving while patient is waiting for the operation and after the operation until the infection completely subsides.

All EN-DCR will be performed under general anesthesia using the mechanical method (including bone punches and drill) for osteotomy. Both mitomycin-C and triamcinolone will be used as adjunctive agents to enhance ostium patency. Bicanalicular intubation with silicone tubes will be done as far as possible.

Outcome measures

Primary:
1. Resolution of symptoms of acute dacryocystitis including pain, medial canthal swelling, epiphora, discharge, associated cellulitis and fever

2. Recurrence of acute dacryocystitis in 3 months

Secondary:

1. Efficacy of EN-DCR
   - Anatomical success, i.e. presence of fluorescence dye in nasal cavity during endoscopic exam at 12 months
   - Functional success, i.e. absence of subjective epiphora at 12 months

2. Safety of EN-DCR – incidence of complications

3. Causative agents of acute dacryocystitis in Hong Kong
Randomisation

- **Sequence generation**
  Block randomization in 3 blocks according to the operating surgeon (HKY, ACW, KKC) in the allocation ratio of 1:1 by computer-generated random numbers of 0 representing the control group and 1 representing the intervention group.

- **Allocation concealment mechanism and Implementation**
  Random numbers in the computer-generated sequence will be placed in sequentially numbered, opaque, sealed envelopes in blocks. These envelopes will be stored in paper box to be kept and managed by a designated clerical staff stationed at the Prince of Wales Hospital/Hong Kong Eye Hospital. Upon consent by the participant to enter the study, the oculoplastics surgeon in charge of the patient will call the designated clerical staff to obtain the randomization code and offer treatment accordingly.

- **Blinding**
  Blinding is not possible for the participant and the surgeon in view of the difference in treatment modality. However, the assessor of the anatomical and functional success at 12 months post-treatment will be blinded to the initial procedures offered.

**Statistical method**
Statistical analyses will be performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL). Descriptive statistics of primary and secondary outcome measures in both groups will be reported. Group means will be compared with independent t-test or Wilcoxon rank sum test. Success rates and complication rates will be evaluated using chi-square test or Fisher’s exact test.

Registration with [www.clinicaltrial.gov](http://www.clinicaltrial.gov)
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Statistical analysis

Statistical analyses were performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL). Group means were compared with independent t-test or Wilcoxon rank sum test. Success rates and complication rates were evaluated using chi-square test or Fisher’s exact test. Pearson’s correlation coefficient was used to determine the degree of correlation. Tests of whether coefficients differed significantly from zero were conducted at the 5% significance level (two tailed).

Sample size calculation

Non-inferiority test

N = 32, control group \((n_1) = 16\), intervention group \((n_2) = 16\)

Formula

\[
n_1 = \left(\frac{z_\alpha + z_\beta}{r\theta_1 (1 - \theta_1) + \theta_2 (1 - \theta_2)}\right)^2 \frac{(\theta_1 - \theta_2 - \delta)^2}{(\theta_1 - \theta_2 - \delta)^2}
\]

\[
n_2 = rm_1
\]

Notations:

\[\alpha = \text{the probability of type I error} = 0.05\]

\[\beta = \text{the probability of type II error} = 0.2\]

\[\theta_1 = \text{expected success rate of intervention group} = 0.7\]

\[\theta_2 = \text{expected success rate of control group} = 0.96\]

\[r = \text{allocation ratio, i.e. } n_2 / n_1, = 1, \text{ for equal allocation.}\]

\[\delta < 0 \text{ for non-inferiority}\]