Pediatric nasolacrimal duct obstruction-benefit of a combined therapeutic approach

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Background: **Pediatric nasolacrimal duct obstruction (PNDO) requires therapeutic intervention after conservative procedures failed. As resilient treatment guidelines for the treatment are missing, the aim of this study was to evaluate the advantages of two different intervention techniques in children with PNDO.**

Methods: **Between January, 2006 and June, 2014, 233 children (0-208 months) were treated either with conventional probing by ophthalmologists only (Group I) or with endonasal endoscopic interdisciplinary approach (Group II). The clinical outcome was analyzed.**

Results: **The overall success rate of Group I was 93.4% compared to 98.4% of Group II (P<0.05). 50% of all interventions (n=62) of Group II required further surgical procedures in addition to probing/irrigation, particularly with regard to children <6 and >24 months.**

Conclusions: **Endoscopic control in treatment of PNDO allows exact identification of the stenosis and appropriate surgical intervention with an improved clinical outcome. Endonasal endoscopic surgical techniques should be the standard PNDO treatment.**

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Key words: **dacryocystocele;**
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Introduction

If canalization of the nasolacrimal duct fails, or the communication between the nasolacrimal duct and the inferior meatus is obstructed, it will result in nasolacrimal duct obstruction. These failures are common and occur in up to 20% of all newborns.[1] However, spontaneous remission or resolution due to non-surgical treatment during the first year of life is described in many cases. 66% of children aged between six and ten months recover with non-surgical treatment within the following six months.[2] Later, spontaneous remission is still possible, but the rate of a positive outcome is considerably lower in the second year of life.[3] Moreover, secondary complications such as recurrent dacryocystitis force the attending pediatrician, ophthalmologist, or ear-nose-throat (ENT) surgeon to early intervention (Supplemental Fig. 1). Usually surgical intervention is recommended close to the age of twelve months if symptoms persist longer than six months and conventional therapeutic procedures failed. However, resilient guidelines are currently missing.[4,5]

If conservative procedures failed, different surgical interventions are described to treat nasolacrimal duct obstruction: office probing, probing under general anesthesia with or without endoscopic control, silicone tube intubation (via naturalis), balloon dacryoplasty or dacryocystorhinostomy with or without silicon stenting. However, there is still a striking lack of consensus in many aspects of the management especially of pediatric nasolacrimal duct obstruction.[4] Usually, the first therapeutic attempts are performed by ophthalmologists only, but more promising and longer lasting results might be achieved in interdisciplinary concepts of ophthalmology and ENT. However, studies with a large number of pediatric cases are missing, and their comparability is hindered due to different surgical techniques, different definitions of success, short period of investigation time and others. Interdisciplinary concepts and the use of endonasal endoscopy logically result in a higher level of effort and costs, which is only justified, if there is a relevant benefit in the clinical outcome.

Therefore, the aim of this study was to analyze the success rates of two different surgical approaches

for children with persisting nasolacrimal duct obstruction after failure of conservative treatment. Widely used conventional probing and irrigation by ophthalmologists only was compared to an endonasal endoscopic controlled interdisciplinary approach in order to investigate differences in clinical outcome or any relevant benefit. Furthermore, we analyzed the performed surgical intervention depending on the age of children to reveal the presumable pathology as a function of age.

Methods

Subjects

This retrospective study included children who underwent probing or surgical intervention for nasolacrimal duct obstruction between January, 2006 and June, 2014. The charts of 246 children treated in the Department of Head Medicine and Oral Health were reviewed. Between January, 2006 and December, 2008 all children had probing or intervention under general anesthesia as an inpatient procedure by an ophthalmologist with irrigation but without endonasal endoscopic control (Group I, non-endoscopic intervention). From January, 2009 onwards, the management was changed. All children received nasolacrimal duct probing/irrigation with endonasal endoscopic control as an inpatient procedure by an ophthalmologist and an ENT surgeon in the ENT clinic under general anesthesia (Group II, interdisciplinary approach: intervention with endonasal endoscopy).

The data included the age and gender of the patients, clinical signs, suspected pathology, treated side, type of intervention and recurrence of nasolacrimal duct obstruction after treatment. All children were referred by ophthalmologists, pediatricians or ENT surgeons to our department due to symptoms suspicious of nasolacrimal duct obstruction: epiphora, recurrent dacryocystitis, or conjunctivitis.

Thirteen children with previous surgical interventions due to nasolacrimal duct obstruction were excluded. The analysis of Group I included 138 patients with a total of 167 conducted interventions (bilateral in 29 cases). Group II included 95 patients with a total of 126 conducted interventions (bilateral in 31 cases) (Fig. 1).

Examinations

All procedures were performed under general anesthesia with uncuffed orotracheal intubation and pharyngeal packing for prevention of aspiration.

Surgical techniques-non-endoscopic intervention (Group I)

After irrigation of the eye with diluted betaisodona (1:10 with saline), the ophthalmologist dilated the upper and lower punctum and inserted a blunt probe for irrigation of the nasolacrimal duct. If reflux occurred at the opposed punctum, the diagnosis of a deep saccal (distally to the common canaliculus) or postsaccal nasolacrimal duct obstruction was verified and no further diagnostic procedure was performed (Supplemental Fig. 2). Assuming that the probe is in contact with the lacrimal bone (hard stop), reflux indicates a saccal or postsaccal stenosis. Otherwise, reflux can also be a consequence of medial common canaliculus stenosis. If there was evidence of a presaccal stenosis of the superior or inferior canaliculus, an external surgical approach was chosen (Toti procedure) and the patients were referred to a different hospital.[6] If not, the blunt probe was then inserted medially through the common canaliculus into the upper part of the lacrimal sac and downwards until bony contact was proved. If forced irrigation was possible, patency of the nasolacrimal duct was assumed. In case of irrigation failure, endonasal opening of the nasolacrimal duct was performed without endoscopic control by forced irrigations or blind punction into the inferior nasal meatus.

Surgical techniques-intervention with endonasal endoscopy (Group II)

Decongestion of the nasal mucosa was achieved using xylometazoline 0.05% gauze for 5 minutes. After irrigation of the eye with diluted betaisodona (1:10 with saline), the ophthalmologist dilated the upper and lower punctum and inserted a blunt probe for irrigation of the nasolacrimal duct. The inferior meatus was inspected under endonasal endoscopic control with a rigid 2.7 mm 0°-endoscope and the inferior turbinate was gently elevated for better view into the

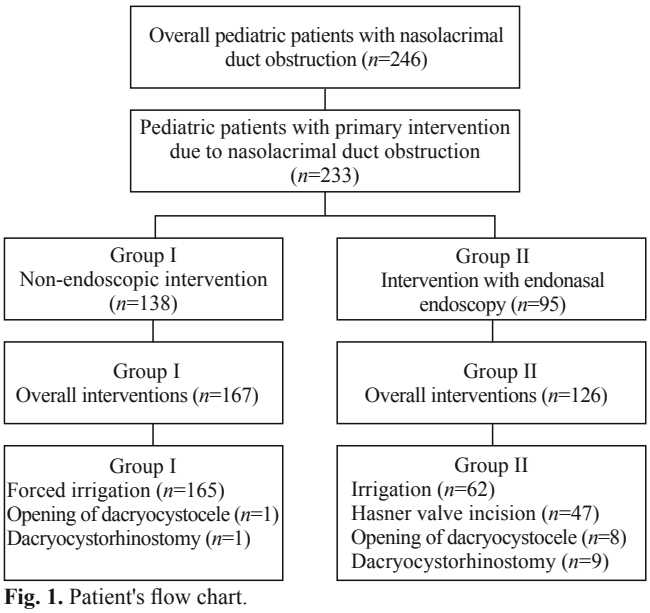

Fig. 1. Patient's flow chart.

area of the Hasner valve. If free endonasal drainage following nasolacrimal irrigation occurred without reflux, no further intervention was performed. If reflux occurred at the opposed punctum, the diagnosis of a deep saccal or postsaccal lacrimal duct obstruction was verified. In case of primary irrigation failure the view on the Hasner valve was optimized by further decongestion and elevation of the inferior turbinate with a freer elevator. If there was a membranous obstruction or protrusion at the Hasner valve, the mucosa was incised with a sickled knife and partially resected until free drainage was possible (Fig. 2). If there was proof of a dacryocystocele, endoscopic cyst marsupialisation with grasping forceps was performed. In case of secondary irrigation failure (following elevation of the inferior turbinate) endoscopic dacryocystorhinostomy was performed by removing the lacrimal bone and the frontal process of the maxilla with a Kerrison punch and by removing the medial wall of the lacrimal sac followed by intubation of a silicone drain (Fig. 2). Our group has described the detailed steps of this procedure in previous studies.[7] Nasal packages were usually not used. If necessary, the fundus was inspected by the ophthalmologist at the end of the procedure. At the end of the procedure an antibiotic eye ointment (ofloxacin) was applied.

Postoperative management

Group I patients underwent a routine clinical examination by an opthalmologist on the first day after surgery. Ofloxacin-containing eye drops were prescribed three times a day for seven days. Group II patients underwent a routine clinical examination by an ENT surgeon and an opthalmologist on the first day after surgery. Ofloxacin-containing eye drops and decongesting nose drops were prescribed three times a day for seven days. Postoperatively, children were seen by their referring opthalmologist/ENT specialist in a private practice. Only if symptoms recurred, the children were rescheduled for an appointment in our clinic. Parents were instructed to reschedule for reprobing if symptoms persisted at six weeks after initial intervention as well. A reprobing or fluorescein dye disappearance test was not performed regularly in case of complete symptom relief for ethical reasons. If dacryocystorhinostomy was performed the silicon intubation drain was removed under general anesthesia followed by an irrigation of the nasolacrimal duct by the ophthalmologist three months after surgery as an outpatient procedure. However, in older children the silicon intubation drain can be removed under local anesthesia as an office-based procedure.

Statistical analysis

The statistical analysis was performed using the statistical program SPSS 20 (SPSS Science, Chicago, IL, USA). Categorical data are reported as proportions (percentage), continuous data are expressed as mean±standard deviation (SD). Chi-square, Fisher's exact test and *t* tests for unpaired groups were used to compare the differences. A nominal P value <0.05 was considered to be statistically significant.

Results

After excluding children with previous intervention for nasolacrimal duct obstruction 233 patients were evaluated. The mean age for all patients was 21.1 months (median: 16 months; SD: 20.96 months; range: 0-208 months). Among them, 113 children were female (48.5%) and 120 (51.5%) children were male. Fifteen patients (6.4%) were younger than six months, 163 (70%) were between six and 24 months old and 55 patients (23.6%) were older than 24 months. Patients suffered from epiphora (n=213; 91.4%), dacryocystitis (n=12; 5.2%), recurrent conjunctivitis (n=6; 2.6%) and status post eye trauma (n=2; 0.9%). A total of 167 patients in Group I and 126 in Group II conducted

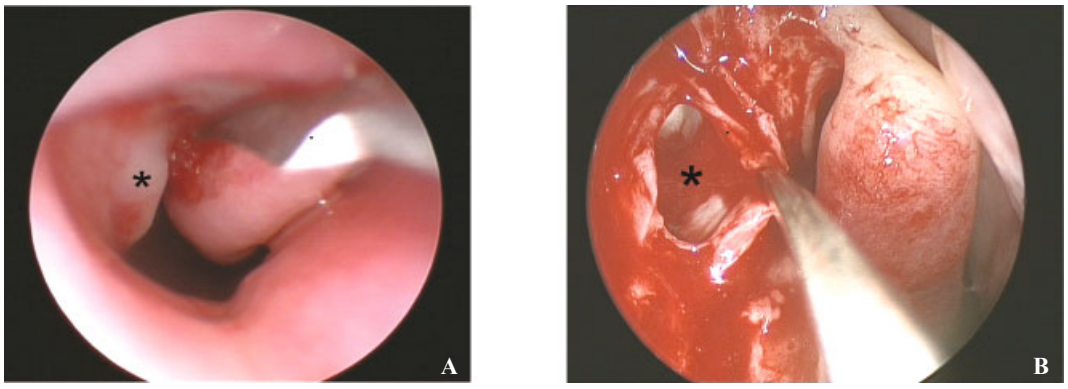

Fig. 2. A: Incision of a membranous occlusion of the Hasner valve (*); **B**: Endoscopic dacryocystorhinostomy with opening of the lacrimal sac (*).

interventions. The mean age in Group I and Group II was 19.83 months and 23.18 months, respectively. In Group I there were 66 female (47.8%) and 72 male (52.2%) patients. In Group II there were 47 female (49.5%) and 48 male (50.5%) patients. In Group I there were 52 left-sided, 57 right-sided and 29 both-sided interventions. In Group II there were 27 left-sided, 37 right-sided and 31 both-sided interventions. The group differences were not statistically different (Table).

In Group I, there were 165 forced irrigations, one opening of a dacryocystocele and one dacryocystorhinostomy. In Group II there were 62 irrigations, 47 incisions of the Hasner valve, eight openings of a dacryocystocele and nine dacryocystorhinostomies.

Non-endoscopic intervention (Group I) resulted in a successful resolution of symptoms in 93.4%. The success rate for Group II was 98.4%. The difference is statistically significant (P=0.046).

Patients younger than six months required significantly more surgical interventions rather than just an irrigation (P=0.0001). Furthermore, the percentage of performed dacryocystorhinostomies increased with the age of children and reached 6.75% in the group of children >24 months (Fig. 3).

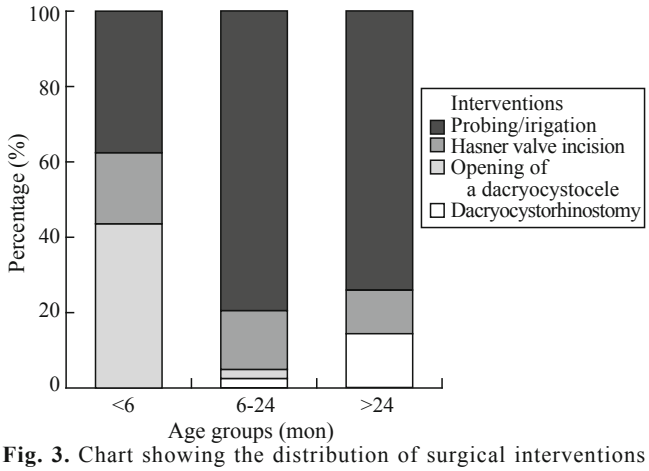

Fig. 3. Chart showing the distribution of surgical interventions depending on the patient's age group (age group <6 mon: surgical intervention necessary *vs*. probing only, P<0.0001; age group >24 mon: DCR necessary in 6.75%). DCR: dacryocystorhinostomy.

Discussion

The symptoms of patients with nasolacrimal duct obstructions are usually obvious. Therefore, it is not necessary to perform any further diagnostics in particular in newborns or toddlers. Moreover, a diagnostic imaging is not indicated. In adult patients, a nasolacrimal duct obstruction can be verified by a fluorescein dye disappearance test or contrast imaging. The delayed drainage of the dye on the affected side can be measured to prove the obstruction. But unfortunately, no conclusion can be made on the localization of the stenosis. However, the knowledge about the localization of the stenosis is necessary to choose the right treatment strategy and thus has importance for the success of treatment.[8] The most common cause of nasolacrimal duct obstruction in young children is a persisting membranous occlusion at the Hasner valve where the nasolacrimal duct drains into the inferior meatus. Even our investigation revealed a Hasner valve obstruction in 37.3% of all cases, with highest rates in the group of children between six and 24 months (Fig. 3).

A surgical intervention for nasolacrimal duct obstruction is recommended only if there are recurrent infections or symptoms persisting longer than six months and conventional therapeutic procedures are ineffective, but resilient guidelines are currently missing. Probing is recommended as initial treatment, but there is no consensus at which age surgical treatment should be performed to achieve best treatment results or whether it is necessary to perform probing/irrigation under endoscopic control or not.[4]

Probing can easily differentiate between postsaccal and presaccal obstruction. This differentiation has high impact on the selection of the surgical procedure. A forced probing may result in misleading of the nasolacrimal duct with consecutive scarring and a high chance of recurrent stenosis. In case of presaccal obstruction an external dacryocystorhinostomy is indicated.[8] Thus, probing has not only therapeutic but also diagnostic significance in nasolacrimal duct obstruction. Regarding probing as the first-line treatment for nasolacrimal duct obstruction, there are two major concerns voiced in the literature. The first concern is whether probing should even be performed in the first place. A prospective randomized trial compared early (office-based) probing with six months of observation

Table. Patient characteristics (n=233)

Variables	Group I (non-endoscopic intervention)	Group II (intervention with endonasal endoscopy)	P value
Patients	138	95	-
Interventions	167	126	-
Age (mon), mean±SD	19.83±21.07	23.18±20.77	NS*
Age (mon), median (range)	15 (0-208)	20 (0-135)	-
Gender (female/male)	66/72	47/48	NS†
Side (left/right/both)	52/57/29	27/37/31	NS†

NS: not significant; SD: standard deviation. *: unpaired t test; †: Chi-square. "-": not compared.

for nasolacrimal duct obstruction.[9] The success rate was 80% for the immediate office-probing group compared to 66% for the observation group. Children in the office-probing group had symptoms resolved three months earlier. Previous publications reported that over 90% of cases with nasolacrimal duct obstruction achieved spontaneous resolution, but success rates of probing lied between 87% and 94%.[1,10] The second concern is at which age probing should be performed. Two issues contribute to this concern: some authors suggest probing between four and nine months of age as office-based probing.[9,11] That means probing is performed avoiding general anesthesia, but resulting in a stressful procedure, which needs to be done very quickly.[12] Therefore, office-probing is mainly performed by experienced pediatric ophthalmologists.[4] However, if probing can be delayed there might be a higher chance of spontaneous remission. This will depend on the age of the child at the initial visit. If a child is between six and nine months old many authors recommend conservative treatment as first-line treatment, whereas surgical intervention under general anesthesia is recommended at the age of 13 months.[4] Our data support the assumption that an intervention (probing with irrigation or surgery of nasolacrimal duct) is highly effective with success rates of 93% and 98%. For our patients-and especially for their parents-office-probing without general anesthesia would not be acceptable. Against the background of the promising spontaneous success rates without any intervention, waiting for spontaneous remission within the first year of life seems to be justified and advisable, if severe clinical complications are not present. Therefore, we suggest nasolacrimal duct probing with irrigation under endoscopic control at the age between 12 and 18 months under general anesthesia for recurrent symptoms of nasolacrimal duct obstruction. Under this clinical situation, probing with irrigation alone will be effective only in about 50% of all cases, which means a poor outcome in every second child if performed without endoscopic control. Simultaneous surgical interventions (e.g., incision of Hasner valve, DCR) are necessary to improve the outcome, and can easily be diagnosed and safely performed using endonasal endoscopic techniques. That means endoscopic visualization of the inferior meatus with elevation of the inferior turbinate and proving sufficient drainage to the inferior meatus by endoscopy. However, 50% of the patients in Group II had no drainage of the irrigation fluid to the inferior meatus. Therefore, endoscopic Hasner valve incision, endoscopic opening of a dacryocystocele or an endoscopic DCR were performed in the same procedure.

The results of this study showed that the success rate of nasolacrimal duct surgery in children was improved by probing/irrigation with simultaneous endoscopic control, which was performed by ophthalmologists and ENT surgeons. In 50% of the cases, free drainage was achieved after elevation of the inferior turbinate only. In 37% of the cases a membranous occlusion of the Hasner valve could be verified and was treated with a precise incision of the mucosa under endoscopic control (overall: 109/126).

In our cohort nine children were treated due to a dacryocystocele. Seven of them were younger than six months, and all could be treated successfully by an endonasal endoscopic approach with no documented recurrent disease.

Furthermore, our data show that there is an increasing probability of endonasal dacryocystorhinostomy due to postsaccal stenosis other than Hasner valve obstructions in children older than two years. In only 2.5% of all treated children between six months and two years a dacryocystorhinostomy was necessary compared to 6.75% of all treated children older than two years. Recurrent inflammation in the nasolacrimal duct cause scarring of the lacrimal drainage system with the result that probing and irrigation cannot be carried out successfully.

We demonstrate that further simultaneous surgical interventions might be necessary particularly in newborns with nasolacrimal duct obstruction due to a dacryocystocele or in children older than two years with the need for dacryocystorhinostomy. Therefore, overall success rates can be improved by specific surgical interventions under endoscopic control in about 5% (93.4% *vs*. 98.4%, P=0.046). Whether the increased success rate of "only" 5% justifies the higher effort of a combined approach by additional endonasal endoscopic techniques, cannot be answered by us yet the results are significant. Nevertheless, simultaneous endoscopic interventions are not possible with conservative probing without endoscopic control.

Success rates for pediatric nasolacrimal duct obstruction vary in the literature depending on observing or performing an intervention, the age of the children at time of intervention and the type of surgical procedure. Unfortunately, there are many different strategies mostly depending on the underlying health care system.[4] Experiences from the treatment of nasolacrimal duct obstructions in adults showed higher success rates by endoscopically controlled interventions.[7] The advantages of endoscopic control are the exact localization and recognition of the cause of the postsaccal obstruction and the controlled opening of the nasolacrimal duct. If necessary, further surgical procedures such as endonasal cyst opening in case of a dacryocystocele may be performed. Additionally, blind probings "via falsa" can be avoided with the reduction of potential recurrent obstructions.

In a large number of cases, our data confirm this assumption. Comparing the success rate in our data there was a significant increase of success following endoscopically controlled interventions compared to non-endoscopic interventions (98.4% *vs*. 93.4%). Data from the literature show similar success rates for nasolacrimal duct surgery in children; 85% to 89% for

endoscopic assisted probing and 87% to 100% for endoscopic DCR.[13-16] The elevation of the inferior turbinate seems to be beneficial to improve drainage into the inferior meatus, which could be shown in every second case. Though, this procedure needs endoscopy and ENT surgeons who are familiar with endonasal surgical techniques from their experiences in sinus surgery or septoplasty.

If conventional treatment fails for uncomplicated nasolacrimal duct obstruction probing under endoscopic control is the treatment of choice.[4] In most cases a forced irrigation solves the obstruction. Although spontaneous resolution and non-endoscopic probing are highly effective in uncomplicated cases, a subset of children clearly profit by the possibility of endonasal endoscopic techniques and concurrent surgery (e.g., newborns with dacryocystoceles and children >2 years with need for dacrycystorhinostomy). In some cases, a simultaneous surgical intervention is necessary. For a symptomatic newborn, a surgical intervention under endoscopic control is very likely to be indicated, rather than probing only.

Advantages of an endonasal endoscopic opening of the nasolacrimal sac into the middle meatus are the preservation of the tear pump by keeping the medial canthal ligament, no external scars and less invasiveness. The approach to remove the lacrimal crest and the medial wall of the lacrimal sac improved the outcome in comparison to burring following transluminal illumination.[7]

In conclusion, probing and forced irrigation as a first-line intervention is effective and solves the problems in about 50% of all cases. Additional endoscopic control of unrestricted lacrimal drainage into the inferior nasal meatus following elevation of the inferior turbinate and simultaneous gentle incision in the region of the Hasner valve in cases of membranous obstruction improve the success rate significantly (+5%).

In our opinion, particularly newborns with clinical symptoms of nasolacrimal duct obstruction at the time of birth and older children (>24 months) are candidates for endoscopic surgical interventions rather than probing/irrigation only, due to the higher chance of dacryocystoceles or postsaccal stenosis other than Hasner valve obstructions. This subset of patients will benefit most from an exact verification of the diagnosis (position of obstruction) by an endoscopic controlled combined approach with the possibility of a concurrent safe surgical intervention with a low morbidity.

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Ethical approval: The study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients prior to surgery.

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Contributors: Fischer M and Mozet C ideated the study, analyzed the data, and wrote the paper. Horn IS and Pirlich M collected and analyzed the data, and revised the paper. Otto M and Dietz A revised the paper.

References

1 MacEwen CJ, Young JD. Epiphora during the first year of life. Eye 1991;5:596-600.
2 Pediatric Eye Disease Investigator Group. Resolution of congenital nasolacrimal duct obstruction with nonsurgical management. Arch Opthalmol 2012;130:730-734.
3 Young JD, MacEwen CJ, Ogston SA. Congenital nasolacrimal duct obstruction in the second year of life: a multicentre trial of management. Eye 1996;10:485-491.
4 Dotan G, Nelson LB. Congenital nasolacrimal duct obstruction: common management policies among pediatric ophthalmologists. J Pediatr Ophthalmol Strabismus 2015;52:14-19.
5 Miller AM, Chandler DL, Repka MX, Hoover DL, Lee KA, Melia M, et al. Office probing for treatment of nasolacrimal duct obstruction in infants. J AAPOS 2014;18:26-30.
6 Weber R, Draf W, Kolb P. Endonasal microsurgical treatment of lacrimal duct stenoses. Indications, technique and results. HNO 1993;41:11-18. [In German]
7 Horn IS, Tittmann M, Fischer M, Otto M, Dietz A, Mozet C. Endonasal nasolacrimal duct surgery: a comparative study of two techniques. Eur Arch Otorhinolaryngol 2014;271:1923-1931.
8 Mozet C, Horn IS, Otto M, Dietz A. Nasolacrimal duct obstruction in children. Children and Adolescents Medicine 2013;13:107-114. [In German]
9 Pediatric Eye Disease Investigator Group. A randomized trial comparing the cost-effectiveness of 2 approaches for treating unilateral nasolacrimal duct obstruction. Arch Ophthalmol 2012;130:1525-1533.
10 Cakmak SS, Yildirim M, Sakalar YB, Keklikci U, Alakus F. Is it necessary to accompany probing with endoscopy in cases of congenital nasolacrimal canal obstruction? Int J Pediatr Otorhinolaryngol 2010;74:1013-1015.
11 Paul TO, Shepherd R. Congenital nasolacrimal duct obstruction: natural history and the timing of optimal intervention. J Pediatr Ophthalmol Strabismus 1994;31:362-367.
12 Schnall BM. Pediatric nasolacrimal duct obstruction. Curr Opin Ophthalmol 2013;24:421-424.
13 Wallace EJ, Cox A, White P, MacEwen CJ. Endoscopic-assisted probing for congenital nasolacrimal duct obstruction. Eye 2006;20:998-1003.
14 Kouri AS, Tsakanikos M, Linardos E, Nikolaidou G, Psarommatis I. Results of endoscopic assisted probing for congenital nasolacrimal duct obstruction in older children. Int J Pediatr Otorhinolaryngol 2008;72:891-896.
15 Kominek P, Cervenka S, Matousek P, Pniak T, Zelenik K. Primary pediatric endonasal dacryocystorhinostomy-a review of 58 procedures. Int J Pediatr Otorhinolaryngol 2010;74:661-664.
16 Saeed BM, Tawalbeh M. Pediatric endoscopic DCR: the outcome in 50 patients. Indian J Otolaryngol Head Neck Surg 2014;66:276-280.

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