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ARTICLE

Do topical ocular antihypertensives affect Dacryocystorhinostomy outcomes: The Coventry experience

Priyanka Mandal[1] · Harpreet Ahluwalia[1,2]

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Abstract

Background It has been suggested that ocular antihypertensives are associated with an increased risk of nasolacrimal duct obstruction. This study aims to assess the effect of topical antihypertensive treatment on surgical outcomes for patients undergoing Dacryocystorhinostomy (DCR) with intubation.

Methods Single centre, retrospective analysis of 170 operations carried out on 144 patients between January 2014 and January 2019. Statistical analysis of DCR failure rates comparing patients on topical ocular antihypertensive treatment and those not on any topical ocular antihypertensive treatment was carried out following medical case record analysis.

Results 6.9% of patients undergoing DCR surgery were on topical antihypertensive treatment. The overall failure rate for all DCR operations during this time period was 11.2%. There was a statistically significant higher rate of primary DCR failure in patients on antihypertensive treatment ($p = 0.02$), with the endonasal DCRs worse affected ($p = 0.01$). The most commonly used topical treatments were carbonic anhydrase inhibitors (CAI, 81.8%), followed by beta-blockers (72.7%). All patients who had failure of primary DCR were using topical beta-blockers and CAI at the time of surgery and post-operatively. There was no statistically significant association between failure rates and the use of preserved or unpreserved drops ($p = 1.0$)

Conclusions Topical ocular antihypertensive treatment may lead to a higher failure rate for DCR surgery due to the provocation of an inflammatory cicatricial response. Beta-blockers and CAIs appear to have the strongest association. Considering a primary external approach in this group as well as switching the class of topical antihypertensive treatment pre-operatively could perhaps improve DCR outcomes.

Introduction

Nasolacrimal duct obstruction (NLDO) can be congenital or acquired. Congenital NLDO most commonly occurs due an imperforate membrane at the valve of Hasner and most cases resolve spontaneously. Primary acquired nasolacrimal duct obstruction is caused by idiopathic inflammation and fibrosis without any identifiable precipitating cause [1]. This leads to partial stenosis or complete NLDO. Secondary acquired NLDO may be caused by infectious processes, identifiable inflammatory conditions, trauma, mechanical disorders or neoplasms [2]. NLDO may also be described in terms of anatomical NLDO with reflux upon syringing, or functional with a patent lacrimal system but persistent symptomatic epiphora.

Adverse reactions to topical ocular antihypertensive treatment are well documented in the literature. Preservatives such as benzalkonium chloride are implicated in ocular surface disease affecting the conjunctiva and cornea [3]. Topical alpha agonists are traditionally associated with inflammatory changes and hypersensitivity reactions [4]. Oral sulphonamide drugs are known to be a potential trigger of Steven Johnson Syndrome [5, 6]. The use of topical Dorzolamide, a sulphonamide derivative, has been directly linked to cases of mucosal inflammatory diseases such as Erythema Multiforme, Toxic Epidermal Necrolysis and Steven Johnson Syndrome [7–10]. This inflammatory process affects the conjunctiva and long-term preoperative use of topical antihypertensives is also associated with a higher rate of trabeculectomy failure [11, 12]. Topical antihypertensives may also affect the nasolacrimal duct mucosa

✉ Priyanka Mandal
priyanka.mandal@nhs.net

[1] Department of Ophthalmology, University Hospitals of Coventry and Warwickshire NHS Trust, Coventry, UK

[2] Professor of Ophthalmology, Aston Medical School, Aston University, Birmingham, UK

in a similar fashion and NLDO has been found with higher prevalence amongst patients on antihypertensive treatment compared to the general population [13, 14].

This study aims to assess whether concurrent treatment with topical antihypertensives affects the surgical outcome of patients undergoing Dacryocystorhinostomy (DCR) surgery with intubation.

Methods

We undertook a retrospective medical case note analysis of all patients who underwent DCR with intubation performed by a single surgeon between January 2014 and January 2019 at the University Hospitals of Coventry and Warwickshire NHS Trust. All patients underwent analysis of their medical records in order to collect data relating to demographics, ocular co-morbidities and surgical outcomes. All patients on topical ocular antihypertensive eye drops at the time of surgery were identified. The full medical case notes of these patients were reviewed in detail especially noting the timing, duration and type of topical treatment used, along with the surgical outcome. This work adhered to the principles of the Declaration of Helsinki.

We defined a successful surgical outcome as resolution of epiphora at post-operative review and anatomical patency of the nasolacrimal system. Patients who were symptomatic with epiphora, but demonstrated anatomical patency were also classed as an unsuccessful outcome along with those lacking anatomical patency.

All the data were tabulated using Microsoft Excel for Mac version 16.7. The data were analysed using SPSS version 22.0 for Windows. The overall percentage failure rates of DCR surgery were calculated for all patients, then subanalysed for assessment of primary DCR failure rates. Fisher exact test was used to calculate statistical significance at a level of 0.05. Further qualitative analysis of the case group was then performed.

Results

A total of 170 Dacryocystorhinostomies with intubation procedures were carried out on 144 patients. Of these, 68% were female and 32% were male. The mean age was 61.5 years ± 17.1 years. The majority of patients (77.1%) were Caucasian, followed by South Asian (16.7%), "Other" (5.6%) and Black (0.6%).

149 operations were primary DCR surgery and 21 operations were DCR revision surgeries. The majority of operations were performed upon patients who had never been on any antihypertensive topical treatment (93.1%, $n =$ 134 patients).

Of the 170 operations performed, 57.1% ($n = 97$) were external DCRs and 42.9% ($n = 73$) were endonasal DCRs. The overall failure rate for all DCR operations during this time period was 11.2% ($n = 19$ operations). There was no statistically significant difference between the overall failure rates of external DCR compared to endonasal DCR ($p = 0.8$).

Primary DCR surgery

One hundred and forty-nine primary DCR operations were carried out on 134 patients, with 15 patients having sequential bilateral surgery during this study period. 63.8% were primary external DCR operations ($n = 95$) and 36.2% were primary endonasal DCR operations ($n = 54$).

The overall failure rate for primary DCR surgery was 11.4% (17/149 operations). There was no statistically significant difference between the overall failure rates for primary endonasal DCR ($n = 6$) compared to overall failure rates for primary external DCR ($n = 11$) ($p = 1.00$).

The failure rates for each group of patients—antihypertensive treatment group vs. control group on no treatment—were compared, and the results are shown in Table 1.

Overall, there was a statistically significantly higher rate of primary DCR failure in patients on antihypertensive treatment ($p = 0.02$). On subanalysis of the groups, the failure rate for endonasal and external DCR in the antihypertensive treatment group was higher than the control group, however this difference only achieved statistical significance in the endonasal group ($p = 0.01$).

Of the 17 patients who had failure following primary DCR surgery, 64.7% ($n = 11$) of these patients went on to have revision surgery with eventual success. Three patients withdrew from follow-up, two patients declined further surgery and one patient was referred on to another clinician

Table 1 Failure rates for primary DCR surgery—antihypertensive group vs. control group.

	Antihypertensive group failure rate %, ($n = 10$)	Control group failure rate %, ($n = 139$)	p value
Overall failure rate (endonasal + external)	40% ($n = 4$)	9.4%, ($n = 13$)	0.02
Endonasal	100%, ($n = 2$)	7.4%, ($n = 4$)	0.01
External	25%, ($n = 2$)	10.1%, ($n = 9$)	0.22

for further review. 23.5% ($n = 4$) of these patients with surgical failure were on topical antihypertensive treatment at the time of surgery.

Revision operations

Of 170 operations performed, 21 were revision operations carried out on 19 patients. The majority of these patients had undergone their primary surgery with our team ($n = 14$) prior to the period we evaluated for this study, two patients had their primary surgery by other clinicians within the trust, two patients were referred from other trusts in the UK and one patient had had their primary DCR surgery abroad.

The majority of patients had undergone initial primary external DCR surgery followed by revision endonasal surgery ($n = 13$, 68.4%). 21.0% of the patients had undergone primary endonasal surgery, followed by revision endonasal surgery ($n = 4$). The remaining patients underwent external revision following primary external DCR surgery ($n = 1$, 5.3%) and external revision following primary endonasal surgery ($n = 1$, 5.3%). Six patients had revision surgery with application of MMC.

Most patients achieved successful outcomes following one revision procedure (16/19, 84.2%) Three patients underwent further second revision surgery. One of these patients (33.3%) was on antihypertensive treatment pre-operatively and post-operatively. All patients eventually achieved successful surgical outcomes.

Topical ocular antihypertensive treatment

Within our study cohort, 11 eyes (6.5%) of 10 patients (6.9%) who underwent DCR during this period were on topical antihypertensive treatment at the time of surgery. Of the 11 eyes, 8 underwent external DCR (72.7%) while 3 underwent endonasal DCR (27.3%). Ten operations were primary DCR surgery whereas one operation was revision surgery whereby the original operation was performed before the study period. These operations are detailed in Table 2 below.

One patient in this group had primary endonasal DCR surgery in 2012 and underwent successful revision surgery during the study period. Of the 11 DCR operations carried out, four were unsuccessful (36.4%) and required further intervention. Within this unsuccessful outcome group, two were primary external DCRs (25%, $n = 2/8$) while two were primary endonasal DCRs (66.7%, $n = 2/3$). Three patients had evidence of dense nasal mucosal scarring at the site of mucosal anastomosis on post-operative nasal endoscopy and subsequently underwent revision surgery whereby one underwent endonasal revision DCR surgery and two underwent external revision DCR surgery. These three patients all eventually achieved successful outcomes. One patient had a patent system with probable narrowing of the anastomosis, which was further evidenced by post-sac delay on lacrimal scintigraphy. The patient is currently considering further treatment.

Patients were taking a range of topical ocular antihypertensive eye drops. The most commonly used topical treatments were carbonic anhydrase inhibitors (CAI) (81.8%%), followed by beta-blockers (72.7%), prostaglandin analogues (54.5%) and alpha agonists (9.1%). At the time of surgery and post-operatively all patients who had failure of primary DCR were using both topical beta-blockers and CAI. There was no statistically significant association between surgical failure rates and the use of preserved or non-preserved antihypertensive treatment ($p = 1.0$).

Discussion

The global prevalence of glaucoma is estimated to be 3.5% [15]. A lot of ophthalmic literature seems to suggest that topical ocular antihypertensive medication and preservatives can trigger cicatricial changes in the conjunctiva [11, 12, 16, 17]. In our study of 144 patients with NLDO, 6.9% of patients were on topical antihypertensive treatment. This might suggest a perhaps higher rate of NLDO amongst glaucoma patients compared to the general population. This is in keeping with findings from other studies [13, 14].

We found a statistically significant and higher failure rate for primary DCR surgery amongst patients on topical antihypertensives compared to those on no treatment at all (40.0% vs. 9.4%). Amongst these patients, nasal endoscopy consistently revealed dense mucosal scarring around the mucosal anastomosis. The failure rate of primary endonasal DCR surgery was higher than the failure rate for primary external DCR surgery in patients on topical antihypertensive therapy. We feel that as endonasal DCR surgery results in an anatomically smaller mucosal anastomosis it may be more significantly influenced by the scarring.

In our study, 81.8% of patients undergoing DCR surgery were concurrently using CAIs prior to and following surgery. Beta-blockers were the second most commonly used topical agent with 72.7% of patients using these. We found that all cases with unsuccessful DCR outcomes were on CAIs and beta-blocker combination formulations. As previously discussed sulphonamides, including topical Dorzolamide, have been linked to mucosal inflammatory diseases [5–10]. Hegde et al. undertook a case review of 13 patients with drug-induced ectropion and found that CAIs were the most commonly used topical treatment amongst this cohort, with 53% of patients on Dorzolamide eye drops [18]. Long-term topical beta-blockers alone as well as in combination with Dorzolamide have been associated with an increased risk of NLDO [13, 14]. Preservatives such as benzalkonium

Table 2 Characteristics and outcomes of patients on topical antihypertensive treatment at the time of Dacryocystorhinostomy surgery.

Patient	Surgery	Treatment at time of surgery	Duration of use	Successful?
60M	Left external DCR	Alpha agonist, β blockers, PG Brimonidine/timolol and latanopros Unpreserved	1 year pre-op (alpha agonist and β blocker), PGA commenced post-op	Yes
63M	Left external DCR	PGA and CA Travoprost and brinzolamid Unpreserved	1 year pre-op	Yes
66F	Right external DCR	PG Latanopros Unpreserved	5 months pre-op	Yes
75F	Left external DCR	PGA + CA Brinzolamide and bimatopros Unpreserved	>10 years pre-op	Yes
81F	Left external DCR	β blocker and CA Dorzolamide/timolo Preserved	5 years pre-op	Yes
69F	Left external DCR	PGA, β Blocker and CA Dorzolamide/timolol and bimatopros Unpreserved	>10 years pre-op	Yes
86M	Right endonasal DCR	β blocker and CA Dorzolamide/timolo Unpreserved	>10 years pre-op	Original surgery in 2012. This re-do surgery was successful.
43M	Left endonasal DCR	β blocker and CA Brinzolamide/timolo Unpreserved	From 2 weeks post-op	No. Found to have scarring on endoscopy. Had re-do external DCR was successful.
69M	Right endonasal DCR	β blocker and CA Dorzolamide/timolo Unpreserved	2 years pre-op	No. Found to have scarring on endoscopy. Had re-do endonasal DCR which was successful.
71F	Right external DCR	PGA, β blocker and CA Dorzolamide/timolol and bimatopros Unpreserved	>10 years pre-op	No. Found to have substantial granulation tissue around ostium and had re-do endonasal DCR twice with eventual success.
76M	Right external DCR	β blocker and CA Dorzolamide and levobunolo Unpreserved	>10 years pre-op	No. Post-sac delay on scintigraphy. Awaiting further review.

M male, *pre-op* pre-operatively, *post-op* post-operatively, *F* female, *β blockers* beta-blockers, *PGA* prostaglandin analogue, *CAI* carbonic anhydrase inhibitor

chloride have been associated with conjunctival inflammation both experimentally and in clinical studies [3, 19]. This creates a possibility that it is the preservative itself, rather than the drug, causing failure. However, in our study we found no statistically significant relationship between DCR failure rates and preserved versus unpreserved antihypertensive topical treatment.

We hypothesise that it is possible that topical ocular antihypertensives, especially CAIs, may trigger fibrosis by a similar mechanism to mucosal blistering diseases and lead to higher rates of NLDO amongst glaucoma patients. The same mechanism may also explain the higher failure rates of DCR surgery amongst glaucoma patients, with fibrosis and cicatrisation at the site of anastomosis. Due to the smaller size of the anastomosis, we suggest that endonasal DCR may be more susceptible to failure in patients using concurrent topical ocular antihypertensive therapy. We wonder whether there is a case to be made for stopping or altering certain topical ocular hypertensives pre-operatively in an attempt to improve outcomes of DCR surgery in this group.

Conclusion

Topical antihypertensives may have a tendency to provoke fibrotic mucosal changes in the nasolacrimal duct. This may explain the higher rates of NLDO in this population compared to the general population. DCR failure rates are also significantly higher amongst patients on topical antihypertensive treatment, with endonasal DCR being especially affected. Consideration of an external DCR approach as well as switching the class of drug and perhaps also using preservative free alternatives may improve surgical outcomes amongst this group of patients.

Summary

What was known before

- It has been suggested that ocular antihypertensives are associated with an increased risk of nasolacrimal duct obstruction. The effect of topical antihypertensives on Dacryocystorhinostomy surgery has been alluded to in the literature.

What this study adds

- Topical ocular antihypertensive treatment may lead to a higher failure rate for DCR surgery. The mechanism may be via an exaggerated cicatricial response in the mucosal tissue which has been pre-treated with these drops. Beta-blockers and carbonic anhydrase inhibitors are the most commonly implicated drops.

Author contributions All authors contributed to the conception of the study, data analysis, revision of the manuscript and approval of the final version. Both authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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