Original Article

Effect of dacryocystorhinostomy on systemic adverse effects of topical timolol maleate

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Purpose: To evaluate whether transformation of the naso-lacrimal passage as happens after dacryocystorhinostomy (DCR) operation has any effect on the systemic adverse effects of topically administered timolol maleate. **Materials and Methods:** Fifty otherwise healthy adult patients without any prior history of cardiac or pulmonary problems scheduled for elective DCR surgery received a drop of timolol maleate 0.5% on the healthy eye. This eye served as a control. Six weeks after successful DCR surgery, the operated eye received the same medication. Parameters compared included intraocular pressure (IOP), pulse rate, blood pressure and forced expiratory volume in the first second (FEV1) findings. **Observations:** Post DCR patients showed an increased incidence of reduced pulse rate and FEV1. **Conclusion:** Timolol maleate ophthalmic preparation should be used with caution in post-DCR patients.

Key words: Dacryocystorhinostomy, intraocular pressure, systemic effects, timolol maleate

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The advent of timolol in 1978 was a landmark as far as glaucoma management was concerned. But in spite of all these accolades, timolol has the drawback of significant systemic side-effects which are attributed to its action on systemic beta receptors.[1]

As beta adrenergic receptors are also located on the cardiac and bronchial musculature, the clinical effects usually pertain to the aforesaid structures and can at times be life-threatening.[2] As systemic absorption occurs mainly through the nasal mucous membrane, suggestions to reduce these effects had been offered as well. Those include digital punctal occlusion and post-medication supine posture for 3–5 min.[3] It was obvious that narrowing of the naso-lacrimal passage as happens during punctal occlusion retards systemic drug absorption, but the effect of accentuation of the aforesaid passage—as might happen after DCR surgery—remained inconclusive.

Aims and Objectives

To find out whether shortening of the naso-lacrimal passage as occurs after DCR surgery has any effect on the absorption and systemic adverse effects of topically applied timolol maleate.

Materials and Methods

Adult patients with unilateral chronic dacryocystitis scheduled for elective DCR surgery were included in this study. The other criteria for selection were:

1. The patients had to have hard stop only, thereby excluding common canalicular obstruction.
2. Diabetics, hypertensives, and patients with other significant systemic diseases were excluded.
3. Patients with any indication of cardiac and respiratory problems were also excluded.
4. Pregnant and lactating mothers were not included.
5. Congenital dacryocystitis cases were not a part of this study.

In all, 66 patients had come for DCR surgery during the designated period, but 16 patients had to be eliminated for the above mentioned reasons.

The unaffected eye served as a control.

On admission a baseline evaluation was done. The unaffected eye then received a drop of timolol maleate 0.5%. Following instillation, the below-mentioned parameters were noted.

1. Intraocular pressure - noted at 30 min, 1 h and 2 h,
2. Pulse rate - noted at 30 min, 1 h and 2 h,
3. Blood pressure - noted at 30 min, 1 h and 2 h,
4. Forced expiratory volume - recorded 2 h after instillation. This is because maximal activity of timolol maleate is noted 2 h after instillation of medication.

Intraocular pressure was measured by Goldman Applanation Tonometry (GAT). Pulse rate, blood pressure were done in real time with the aid of a pulse oxymeter. FEV1 was done in consultation with the department of chest medicine.

Results of this situation were classified as Situation A or control situation.

Six weeks after DCR surgery—when it was ensured that the surgical anastomosis was patent—the operated eye received a similar medication as stated before, that is a drop of timolol

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maleate 0.5%. The aforesaid parameters were noted again and compared with the baseline readings.

Results of this situation were classified as Situation B or study situation.

The same brand of timolol maleate was used in the entire study to eliminate bias. Informed consent was taken from all participants of this study. Appropriate permission was taken from the institutional ethics committee.

Comparative statistical analysis of the entire data was done by Z test. The Z test, quite like the t test is a test of significance, meaning that they are mathematical methods by which the probability or relative frequency of an observed difference occurring by chance is found. However, when the sample size is larger than 30 and the data is quantitative, Z test is preferred. Hence in this study where 50 patients were involved in both groups, Z test was applied to find out the *P* values.[4]

Results

This study was done in tertiary setup over a period of approximately one and a half years. Among the 50 patients enrolled in this study, 40 were females and 10 were males. Thirty patients had naso lacrimal duct obstruction in the right eye and 20 patients had it in the left eye [Table 1].

1. **Intraocular pressure (IOP)**: The mean IOP of 50 patients before application of any medication in the control situation was 14.8 mmHg. Readings in both situations were taken at ½ h, 1 h and 2 h intervals after application of medication.
   In Situation A the mean IOP at the designated intervals were 12.8 mmHg, 10.9 mmHg and 10 mmHg.
   In Situation B the corresponding readings were 12.4 mmHg, 10.8 mmHg and 10.8 mmHg.
   On comparison, *P* values during ½ and 1 h were not significant, but at the end of 2 h *P* value was less than 0.01, which was statistically significant.
2. **Pulse rate**: The mean pulse rate (PR) of 50 patients before application of any medication was 78.8/ min. Readings were similarly taken at ½ h, 1 h and 2 h intervals after application of medication.
   In Situation A, the mean readings after application of medication were 76.2/ min, 72/ min and 67.8/ min. Corresponding readings in Situation B were 66.4/ min, 61.0/ min and 56.4/ min.
   P values at ½ h, 1 h and 2 h were all significant, $P \simeq 0$, (<0.000…)
3. **Blood pressure**: The mean blood pressure pre medication in this study was 116/76 mmHg. In the control situation, no significant change in blood pressure was observed after timolol administration. In the study situation, which is after DCR operation, timolol application did cause a slight reduction in blood pressure in the majority of the subjects, and the recorded mean was 114/76 mmHg. This was however not found to be of any clinical or statistical significance.
4. **Forced expiratory volume in the first second (FEV1)**: A normal person expels 75–80% of his total expiratory volume in the very first second itself—something which is clinically recorded as FEV1 (forced expiratory volume in the first second) during spirometry.[5] The mean FEV1 of 50 patients before administration of any medication was 80.2% in this study. In Situation A, the mean FEV1 2 h after timolol instillation was 66%. In Situation B, the mean FEV1 after the same period was 46.4%. *P* value in this situation was <0.05, which was statistically significant.

Table 1: Mean values and standard deviation of included intraocular pressure, pulse rate and forced expiratory volume in the first second. As changes in blood pressure in the two study situations were not clinically or statistically significant, it was not included in the table

Parameter	Time	Mean of A	Mean of B	Std dev of A	Std dev of B
IOP	½ H	12.84	12.4	1.404948	1.761261
	1 H	10.92	10.8	1.724257	1.616244
	2 H	10.00	10.8	0.989743	1.616244
Pulse rate	½ H	76.2	66.4	4.105745	3.917517
	1 H	72.0	61.0	7.045045	3.984664
	2 H	67.8	56.36	10.07928	6.229489
FEV1	AT 2 H	66 %	46.44 %	1.564921	5.329930

IOP: Included intraocular pressure, FEV1: forced expiratory volume in the first second

Discussion

Timolol is a non-selective beta receptor antagonist without any intrinsic sympathomimetic activity or membrane-stabilizing activity. It is usually dispensed in a bottle that delivers approximately 39 μL in a single drop.[2,6] Systemic effects are reasonably common and hence it is expected that the latter shall be clinically as evident as ocular effects.[5]

The basic IOP-lowering effect of timolol in Situation B was significantly less than situation A (*P*<0.01). This was perhaps due to the fact that the shortened naso-lacrimal passage as occurs after DCR surgery offers a faster elimination of the medication from the conjunctival sac and the nasal mucous membrane.

The change in two systemic parameters were more apparent—pulse rate and FEV1. None of the patients, however, had any subjective complaints regarding the decrease in pulse rate, but the phenomenon must be kept in mind while administering beta blockers to susceptible patients.[5,6]

The reduction in FEV1 was more apparent. As the respiratory effects of timolol are maximum after 2 h of administration of medication, the FEV1 was done during that period.[7,8] A noticeable change in FEV1 was seen in both the groups.[8,9] A *P* value <0.05 emphasizes the enhanced bronchial activity of timolol in post-DCR situations.

It was felt that topical administration of timolol should be done with caution in post-DCR patients. The shortening of the naso-lacrimal passage as occurs after DCR surgery perhaps offers a quicker highway for transport of ocular medications to the nasal mucous membrane thereby causing greater systemic absorption. Where application is mandatory, appropriate precautions should be taken to prevent its egress beyond the lacrimal canaliculi by means of digital punctal occlusion. The participation of a physician in the therapeutic process might also be considered in such a scenario.

Conclusion

In conclusion, it should be reiterated that DCR surgery offers an altered naso-lacrimal anatomy and hence drug transportation and absorption in that location is expected to change. The consequences that such an alteration might have on the pharmaco-dynamics of a drug with systemic adverse effects like timolol should be kept in consideration before its administration.

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