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Research Article

# Comparison of the Clinical Profiles of Patients with Childhood Glaucoma Based on Refractoriness to Angular Surgery in a Public Hospital in Brazil

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## ABSTRACT

**Objective:** This study aims to provide more information about childhood glaucoma by comparing the profile of refractory and non refractory cases to angular surgery in a public hospital in Brazil.

**Methodology:** Retrospective cross sectional study carried out by collecting data from electronic medical records of all patients under 18 years of age who underwent surgical procedures for glaucoma between August 1, 2018, and January 31, 2021, in a childhood glaucoma department of a public hospital in Brazil. For this study, refractory childhood glaucoma included children who failed to respond or responded poorly to surgical angle procedures. Surgical success was defined as intraocular pressure equal to or less than 21 mmHg and greater than 5 mmHg with or without glaucoma medications. Failure was defined as intraocular pressure being outside of the successful range on two consecutive visits. The profiles of refractory and non refractory patients were compared according to the following data: Gender; age, laterality and type of glaucoma, clinical history, family history of glaucoma, procedures performed, intraocular pressure levels, ocular axial length, horizontal diameter and corneal opacity, vertical cupping of the optic nerve, presence of postoperative complications requiring intervention surgical.

**Results:** Most refractory eyes belonged to male patients (71%), with bilateral glaucoma (93%), of the primary type (93%, p=0.02). They had lower IOP at the end of the study (11.85 mmHg; p=0.007), had no variation of the vertical cupping of the optic disc from the preoperative to the end of study (p=0.02), and more postoperative complications (28.6%; p=0.02). All fourteen refractory eyes had IOP below 18 mmHg at the end of the study and 53% of them required hypotensive eye drops.

**Conclusion:** The present study proved that angular surgery, when possible, is the best initial surgical option, resolving most cases with fewer complications than filtering surgeries. More prospective data is needed to improve the surgical management of childhood glaucoma.

**Keywords:** Infantile glaucoma; Trabeculotomy; Implant for glaucoma drainage; Cryotherapy

## INTRODUCTION

Childhood glaucoma is an eye damage related to Intraocular Pressure (IOP) that occurs in childhood. In addition to the increased cup disc ratio and the visual field defect consistent with glaucomatous optic neuropathy, the definition of childhood glaucoma also reflects the effect of IOP on other ocular structures, such as increased ocular axial diameter and haab striae.

According to the 9th consensus of the world glaucoma association, published in 2013, childhood glaucoma can be classified as primary or secondary glaucoma. The primary type includes Primary Congenital Glaucoma (PCG) and Juvenile Open Angle Glaucoma (JOAG). The secondary type includes glaucoma associated with acquired condition, following cataract surgery, associated with non acquired ocular anomalies, and associated with non acquired systemic anomalies [1].

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The treatment of childhood glaucoma is mainly surgical [2]. Topical medication may be needed for additional IOP control following surgery or as a temporary measure until the procedure is performed [3]. Goniotomy is the procedure of choice whenever the transparency of cornea allows visualization of the camerular sinus. Trabeculotomy (TRO) can be performed in all cases. Recent studies have been showing that TRO seems to be superior to goniotomy in primary congenital glaucoma [4]. Surgical alternatives are Trabeculectomy (TREC), Implantation of Drainage Devices (IDD) and cyclodestructive procedures.

Traditionally, many ophthalmologists recommend a "staged approach", which involves starting with angle surgeries, repeating them in case of failure. The procedures can be followed by TREC or IDD for refractory patients or cyclodestruction for patients with very advanced glaucoma [5]. In children with poor prognosis childhood glaucoma or prior failed angle surgery, TRO can be combined with TREC (TRO-TREC) [6]. Some authors have suggested primary IDD for cases in which angle surgery is unlikely to succeed [7].

Although angle based surgeries are the gold standard treatments for Primary Congenital Glaucoma (PCG), more than 20% of these surgeries will eventually fail. Sex, phenotype of glaucoma and stage of presentation may be contributing factors for failure. There is little information about children who fail to respond or respond poorly to initial surgery for childhood glaucoma [8]. This study aims to provide more information about childhood glaucoma by comparing the profile of refractory and non refractory cases to angular surgery in a public ophthalmology hospital in the state of Bahia, Brazil.

## MATERIALS AND METHODS

This is a retrospective cross sectional study carried out by collecting data from electronic medical records of all patients under 18 years old who underwent surgical procedures for glaucoma from August 1, 2018 to January 31, 2021, at university hospital professor Edgard Santos, a public hospital in the state of Bahia, Brazil.

The clinical epidemiological profile of refractory and non refractory patients to angular surgery was compared. The investigated data included: Gender; age, laterality and type of glaucoma, medical history, family history of glaucoma, procedures performed, intraocular pressure levels, ocular axial length, horizontal diameter and corneal edema, vertical cupping of the optic nerve, presence of postoperative complications requiring surgical intervention, and loss of medical follow up. The preoperative IOP measurements reported were collected from the examination performed in the operating room prior to the patient's first surgery, and the end of the study was obtained in an examination under sedation, at least between three to six months postoperatively. All IOP measurements were performed under sedation with a perkins application tonometer. The assessment of papillary excavation was performed with indirect binocular ophthalmoscopy, in the same pre and postoperative situations as for tonometry. The horizontal corneal diameter was measured with a surgical caliper and the ocular axial length was measured using contact ultrasonic biometry with a quantel medical compact touch ultrasound. This measurement was transferred to the ocular axial growth curve (in millimeters) by age (in months) adapted from the study by Sampaolesi to determine the percentile ranges.

The angular surgery performed was TRO in all patients according to the technique described by mcpherson [9,10]. In patients who underwent valve implantation, the Ahmed FP7 valve was used. At the end of the surgery, sub tenon antibiotics and steroids were injected in all cases. The postoperative regimen included combined topical eye drops of 0.3% tobramycin and 0.1% dexamethasone (four times daily for one week, then twice daily for one week and once daily for one week).

In this study, childhood refractory glaucoma includes children who failed to respond or responded poorly to angle surgical procedures. Surgical success was defined as IOP less than or equal to 21 mmHg and above 5 mmHg with or without glaucoma medications. Failure was established when IOP was out of success ranges on two consecutive visits, while on anti-glaucoma medication. Eyes that underwent TRO during the study period and required IDD later, still during the study period, had their data analyzed in the refractory group.

This study adhered to the ethical principles outlined in the declaration of Helsinki and was approved by the research and ethics committee of the university hospital professor Edgard Santos. All numerical and categorical data was stored in the GNU PSPP software, version 1.4.1, for processing, descriptive analysis, and presentation of results in graphs and tables. The comparison between quantitative variables was performed using the T test and categorical data using pearson's *chi-square* test. P values less than 0.05 were considered statistically significant.

## RESULTS

### General profile

From August 1, 2018, to January 31, 2021, a total of 53 patients under the age of 18 underwent surgical procedures for childhood glaucoma at the university hospital professor Edgard Santos, in the state of Bahia, Brazil. Of these, 18 (34%) patients were female and 35 (66%) were male. Mean age at first glaucoma surgery was 11.7 months (standard deviation ± 19.65, confidence interval 1 to 103 months). More than half of the patients (52%) were operated up to five months of age. Only six (11.3%) patients had a positive family history of glaucoma. Regarding the laterality of glaucoma, 32 (60.4%) patients had bilateral glaucoma and 21 (39.6%) had unilateral glaucoma. Thirty five patients (66%) had primary glaucoma and 18 (34%) had secondary glaucoma. The 35 patients diagnosed with glaucoma of the primary type had PCG, no case of JOAG was detected. Among patients with secondary type glaucoma, one was acquired, four were associated with congenital cataract, five were associated with ocular abnormalities, and eight were associated with systemic diseases (Table 1).

**Table 1:** Clinical and epidemiological characteristics of the total sample of patients.

| **Number of patients** | **53** |
|---|---|
| **Gender** | |
| Feminine | 18 (34%) |
| Masculine | 35 (66%) |
| Age at first surgery (average in months) | 11.7 ± 19.7 (1-51) |
| **Family history** | |
| Positive | 6 (11.3%) |
| Negative | 18 (34%) |
| Undetermined | 29 (54.7%) |
| **Laterality** | |
| Unilateral | 21 (39 .6%) |
| Bilateral | 32 (60.4%) |
| **Type** | |
| Primary | 35 (66%) |
| Secondary | 18 (34%) |
| **Secondary type** | |
| Acquired condition | 1 (5.6%) |
| Following cataract surgery | 4 (22.2%) |
| Associated with non acquired ocular anomalies | 5 (27.8%) |
| Associated with non acquired systemic anomalies | 8 (44.4%) |

Seventy two eyes of the 53 patients underwent surgical procedures for glaucoma during the study period. Preoperative, these eyes had a mean tonometry of 26.2 mmHg (standard deviation ± 7.1 and confidence interval 16 to 50), a horizontal corneal diameter of 13.8 mm (standard deviation ± 0.9) and, in cases where the cornea allowed visualization of the posterior segment, vertical cupping of the optic disc of 0.8 (standard deviation ± 0.2). The ocular axial length (in millimeters) was standardized by age (in months), according to the ocular growth curve adapted from the study by Sampaolesi and presented in percentile intervals. Of the eyes that underwent preoperative biometry, 93.3% (n=42) had a percentile above 50, and 64.4% (n=29) had a percentile above 95. Corneal edema was characterized in intensities ranging from 1 to 4 crosses. Of the eyes that had estimated corneal edema, the intensity of 2 crosses (30.5%, n=18) was the most frequent in the preoperative period (Table 2).

**Table 2:** Clinical characteristics of the total sample of eyes studied.

| **Number of eyes** | **72** |
|---|---|
| **Preoperative tonometry (mmHg)** | |
| Average | 26.2 ± 7.1 (16 a 50) |
| **Preoperative corneal diameter (mm)** | |

| | |
|---|---|
| Average | 13.8 (± 0.9) |
| **Preoperative vertical cupping of optic nerve** | |
| Average | 0.8 (± 0.2) |
| **Preoperative ocular axial length per age (average in percentile)** | |
| P>95 | 29 (64.4%) |
| P=50 a 95 | 13 (18.1%) |
| P=5 a 50 | 2 (2.8%) |
| P<5 | 1 (1.4%) |
| **Preoperative corneal opacity (average)** | |
| 1+ | 15 (20.8%) |
| 2+ | 18 (25%) |
| 3+ | 11 (15.3%) |
| 4+ | 15 (20.8%) |
| **Tonometry at the end of study (mmHg)** | |
| Average | 13.9 ± 4.5 (6 a 30) |
| **Vertical cupping of optic at the end of study** | |
| Average | 0.8 (± 0,2) |
| Delta[1] tonometry (mmHg) | 11.6 ± 6,8 (-2a27) |
| Delta[1] cupping | 0.08 (± 0.1) |
| **Refractoriness to angular surgery** | |
| Yes | 15 (20.8%) |
| No | 50 (69.4%) |
| Did not undergo angular surgery | 7 (9.7%) |
| Angular surgery success rate | 76.92% |
| Tonometry>21 mmHg at the end of study | 2 (2.8%) |
| Tonometry<21 mmHg at the end of study | 70 (97.2%) |
| **Amount of angular surgery** | |
| 0 | 7 (9.7%) |
| 1 | 36 (50.0%) |
| 2 | 23 (31.9%) |
| 3 | 6 (8.3%) |

| | |
|---|---|
| Surgical complications | 7 (9.8%) |

**Note:** [1]One-variable delta=average of the variable in the preoperative-average of the variable at the end of study.

At the end of the study, the mean eye tonometry was 13.9 mmHg (standard deviation ± 4.5, confidence interval 6 to 30), which meant a mean reduction of 11.6 mmHg (standard deviation ± 6, 8 confidence interval from -2 to 27). The mean vertical cupping of the optic disc at the end of the study was 0.8 (standard deviation ± 0.2), which meant a mean reduction of 0.08 (standard deviation ± 0.1). Fifteen eyes (20.8%) were refractory to TRO and required filtering or cyclodestructive procedures for adequate IOP control. Fifty eyes (69.4%) had adequate IOP control after one or more TRO. Seven eyes (9.7%) did not undergo TRO as initial surgical treatment. Considering only the eyes submitted to TRO, the success rate of this angular surgery was 76.9%. Only 1 eye (1.9%) had IOP above 21 mmHg at the end of the study. Only seven eyes (9.8%) had surgical complications.

## Compared profiles

For this comparative analysis, eight eyes of eight patients were excluded. Of these patients, seven did not undergo angular surgery as the first surgical choice: Four were submitted to TRO-TREC at the surgeon's preference, three of them had PCG, and one had glaucoma secondary to orbital neurofibroma and type 1 neurofibromatosis; two eyes were submitted to IDD as the first option, being one case of glaucoma after cataract surgery and another case associated with Klippel-Trenaunay-Weber syndrome; one eye was submitted to cryotherapy with no visual prognosis due to cataract, pupillary seclusion, acute angle closure glaucoma and athalamia after probable uveitis. Another eye with PCG and a history of severe ocular trauma was also excluded from the comparison due to the difficulty to classify glaucoma. Thus, 64 eyes of the remaining 45 patients were compared.

Sixty four eyes were divided into two groups, according to the presence or absence of refractoriness to angular surgery. Fourteen eyes were included in the refractory group (22%) and 50 were included in the non refractory group (78%). In both cases, most of the patients were male (10 patients, 71% refractory glaucoma and 32 patients, 64% non-refractory glaucoma, p=0.06). There was no statistical difference in the mean age reported at the first surgery, which was 5.7 ± 3.4 months among refractory cases and 7.7 ± 10.2 months among non-refractories (p=0,12). Among refractory patients, 93% had bilateral glaucoma (13 patients). Among the non-refractory, this percentage was 68% (34 patients), p=0, 06. Refractory glaucoma (13 patients) was diagnosed with PCG in 93% of cases. Among the non-refractory, this proportion was 60% (30 patients), p=0, 02 (Table 3).

**Table 3:** Comparative profile between eligible eyes regarding refractoriness of angular surgery.

| | Refractory to angular surgery (n: 14) | Non refractory to angular surgery (n: 50) | P-value |
|---|---|---|---|
| Preoperative tonometry (average in mmHg) | 28.0 ± 4.6 | 25.6 ± 8 | 0.08[1] |
| Preoperative vertical disc cupping (average) | 0.9 ± 0.1 | 0.8 ± 0.2 | 0.33[1] |
| Tonometry at the end of study (average in mmHg) | 11.9 ± 1.9 | 13.7 ± 3.9 | 0.007[1] |
| Vertical cupping at the end of study (average) | 0.9 ± 0.1 | 0.7 ± 0.2 | 0.12[1] |
| Delta[3] tonometry (in mmHg) | 15.9 ± 4.6 | 10.8 ± 7.0 | 0.15[1] |
| Delta[3] vertical cupping | 0.0 ± 0.0 | 0.1 ± 0.2 | 0.02[1] |
| Postoperative complications | 4 (28.6%) | 3 (6.0%) | 0.02[2] |
| Use of eye drops at the end of study | 8 (57.1%) | 24 (48.0%) | 0.55[2] |

**Note:** [1]T test for independent variables ; [2]Pearson's *chi-square* test; [3]One-variable delta=Average of the variable in the preoperative-Average of the variable postoperative.

There was no statistical difference between refractory and non refractory eyes considering the following variables: Preoperative tonometry, vertical cupping of the optic disc from preoperative to the end of study, variation in tonometry throughout the study and use of eye drops at the end of the study, although these data presented a very small number of patients for analysis.

Final IOP was lower (p=0.007) in refractory eyes (mean IOP of 11.85 mmHg, standard deviation ± 1.91, n=13 eyes) than in non refractory eyes (mean IOP of 13.65 mmHg, standard deviation ± 3.94, n=46 eyes).

All fourteen eyes in the refractory glaucoma group had a final IOP below 18 mmHg. Among the non refractory, 39 (78%) had IOP below 18 mmHg, ten (20%) between 18 and 21 mmHg and one (2%) had IOP greater than or equal to 21 mmHg. Fifty three percent of eyes refractory to angular surgery required hypotensive eye drops at the end of the study (8 eyes). Among non-refractory eyes, 48% were using eye drops at the end of the study (24 eyes). Among the refractory eyes, four (28.6%) had complications, being one case of athalamia, one of tube displacement, one of cataract and one of hyphema. Among the non refractory eyes, two (4%) had hyphema requiring anterior chamber lavage.

## DISCUSSION

To our knowledge, this was one of the first studies in the Brazilian population comparing the clinical profile of patients with childhood glaucoma based on refractoriness to angular surgery. The general profile of 53 cases of childhood glaucoma operated within 30 months in a public hospital was described. Most patients had glaucoma control after one or more angular surgery and were classified as non refractory to angular surgery. Male sex prevailed both among refractory and non refractory patients. A decrease was observed between the mean of the vertical excavation measured before and after the operation in non refractory cases. The number of complications was higher among refractory cases.

For this study, pediatric glaucoma was considered refractory when there was failure or poor response to eye pressure control after initial angular surgery, regardless of how many angular surgeries were performed. This classification was adapted from the review article published in 2020 on surgical techniques in childhood glaucoma. Eight cases in which angular surgery was not the first option and other procedures were performed directly were not included in this analysis due to lack of information for surgical choice.

In this sample, both refractory and non refractory patients had a higher frequency of primary congenital glaucoma. Although rare, PCG is the most common type of childhood glaucoma, with bilateral manifestation in 75% of cases. It is a severe form of glaucoma and is usually transmitted as an autosomal recessive disease with incomplete penetrance. Its incidence is higher in communities with high rates of consanguinity. This makes the disease more common and severe in the Middle East than normally seen in Western countries. Three genes have been shown to be involved in the development of GCP: CYP1B1, LTBP2 (latent protein binding factor beta 2) and TEK (receptor tyrosine kinase). The proteins encoded by these genes play an important role in this disease that is still unclear [11].

Among refractory and non refractory patients, most were male. Although PCG is more frequent in males, studies associate females with a lower success rate in trabeculotomy and lower IOP reduction [12]. Bilateral glaucoma was more frequent among eyes with refractory glaucoma, which agrees with El Sayed's findings, who reported lower pressure reductions and lower ORT efficacy among cases of bilateral disease.

When comparing angular surgery refractory eyes with non refractory eyes, there was no difference in mean age at first surgery. In the literature, some studies point to angular surgery performed after 2 years of age as a risk factor for failure, but the age of onset of the disease and the complexity of the case are also important. The earlier the onset of glaucoma, the worse the prognosis, the more severe the case and the higher the failure rate. An early presentation of glaucoma in children suggests a more immature angle, which may compromise the outcome of angle surgery [13]. As in our refractory patients, the majority were from PCG, this hypothesis could explain why the mean age of these patients was lower than the non-refractory ones. It is known that some children already begin to have signs of intrauterine eye growth, while others show the first signs up to two years of age, when it is considered late childhood glaucoma.

The increase in ocular pressure and the vertical diameter of the papillary excavation of the optic disc are classic parameters of the severity of the disease as well as the increase in corneal diameter, the decrease in corneal transparency and the increase in axial length [14]. In this study, only the difference between the preoperative and postoperative cupping measurements showed a difference between the groups. A decrease in vertical cupping was observed in the eyes of non-refractory patients. This decrease has been observed in some studies that evaluated childhood glaucoma [15]. However, there are studies with optical coherence tomography that show that, even with the involution of the excavation, the damage to the retinal nerve fiber layer can remain [16].

Lower postoperative IOP was found among refractory eyes. This result may be related to the fact that the study was cross sectional. Patients with higher IOP could still switch to the refractory group in the event of a longer follow up. Studies that had similar findings showed that higher preoperative IOPs lead to greater postoperative reduction, but these cases were associated with a higher rate of surgery failure [17].

Our study confirms that more complications occur in eyes that underwent filtering surgery. A Romanian study presented hyphema as the only postoperative complication in patients undergoing ORT (78.95% of cases). This same study also showed that preoperative IOP of 25 mmHg or greater is predictive (p=0.023) for postoperative hyphema, and preoperative IOP of 28 mmHg or greater is predictive (p=0.02) for the need for intervention [18]. In the present study, only hyphemas that required surgical intervention for resolution were considered as complications. A study that evaluated the characteristics of pediatric glaucoma in a Latin American hospital reported endophthalmitis, hyphema, tube

displacement, vitreous prolapse and hyper filtering blister as a complication of TRO-TREC [19]. An Iranian study reports postoperative complications in 23% of eyes with GCP undergoing IDD, including tube displacement, endophthalmitis, suprachoroidal hemorrhage, and progression of glaucomatous optic neuropathy.

Finally, this study had some limitations. Axial length only started to be measured routinely in 2018 in our service, which limited preoperative information in most cases. The lack of complete information in some medical records made it impossible to do a comparative analysis of some variables. This reinforces the need for a standardized registration system, as recently implemented at the university of Sao Paulo in the pediatric glaucoma department. This perspective is being considered for our hospital.

## CONCLUSION

The present study therefore proved that angular surgery, when possible, is the best initial surgical option, resolving more than half of the cases with fewer complications than filtering surgeries. Therefore, repeating the angular approach in another location, in cases of insufficient IOP decrease after the initial surgery, proved to be a safer option than the immediate performance of filtering surgeries. The need for further studies on the surgical management of childhood glaucoma is reinforced, especially for children who did not achieve adequate blood pressure control after the initial surgeries.

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