Title: Long Term Outcomes of Trabeculectomy Augmented with Mitomycin-C Undertaken within the First Two Years of Life

Running Head: MMC Trabeculectomy within the First Two Years of Life

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No conflicting relationship exists for any author and all have no proprietary or commercial interest in any materials discussed.

Précis

Contemporary pediatric trabeculectomy technique with mitomycin-C in phakic infants with glaucoma can be associated with long term IOP control off medications and with satisfactory visual outcomes.

Abstract

Purpose: To evaluate the long-term effectiveness and safety of mitomycin-C (MMC) augmented trabeculectomy undertaken within the first two years of life for the surgical management of glaucoma.

Design: Retrospective, consecutive, non-comparative case series.

Participants: All children who underwent MMC augmented trabeculectomy within two years of birth between May 2002 and November 2012.

Methods: The medical records of 40 consecutive eyes of 26 children who underwent surgery by a single surgeon were reviewed. Data collected during routine clinical care were analyzed.

Main Outcome Measures: Assessment of clinical outcomes included intraocular pressure (IOP), final visual acuity, bleb morphology, surgical complications (early and late), postoperative interventions and further glaucoma surgery performed. Surgical success was defined as 5mmHg ≤ final IOP ≤ 21mmHg, with anti-glaucoma medications (qualified success) and without (complete success), stable ocular dimensions and optic disc cupping, no further glaucoma surgery (including needling) or loss of light perception. Surgical outcomes were evaluated using Kaplan-Meier life-table analysis.

Results: 40 eyes of 26 children were studied over a mean follow up period of 62.8 months. The majority of cases (80%) were primary congenital glaucomas following failed goniotomy surgery. Cumulative probabilities of survival at 1, 5 & 7 years were 78%, 67% and 60% respectively. Of eyes regarded as successful, 96% (25/26 eyes) had controlled IOP off topical medication, and 44% achieved visual acuity of 20/40 or better. Only one of the 40 eyes developed a cystic avascular bleb with all the other eyes being non-cystic in nature (diffuse and elevated or flat) at final follow up. Sixty-four percent (9/14 eyes) of cases regarded as failures ultimately underwent glaucoma drainage device implantation.

Conclusions: Contemporary pediatric trabeculectomy technique augmented with MMC is an effective procedure in the management of glaucoma within the first two years of life, as shown by the successful long-term outcomes and low incidence of sight threatening complications. Trabeculectomy, following failed goniotomy surgery, or as a primary surgical intervention may offer a phakic infant with glaucoma an excellent opportunity to achieve long-term control of intraocular pressure off medications and be associated with optimal visual outcomes.

1 Introduction

Childhood glaucoma is an uncommon disorder characterized by elevated intraocular pressure (IOP) related damage to the eye that can be caused by a diverse group of conditions. The ultimate therapeutic goal in children with glaucoma is to provide a lifetime of vision, for which successful control of IOP is crucial. Medical therapy plays an important role in controlling IOP but the mainstay of treatment is surgery, which usually needs to be repeated[1-4]. Surgical intervention is often the case for glaucoma presenting in infancy, that is within the first two years of life. The surgical procedure of choice is largely determined by the type of glaucoma and may be further influenced by factors such as corneal clarity and the surgeon's experience and practice. The outcomes and longevity of surgical interventions may have a significant impact upon the future quality of life of both children and their families[5].

Primary congenital glaucoma (PCG) is the commonest glaucoma in infancy[1, 4] for which angle surgery (goniotomy or trabeculotomy) is widely regarded as the primary surgical intervention of choice[6] due to successful reported outcomes[7-9]. Poorer outcomes from angle surgery are usually reported for secondary childhood glaucomas[10, 11]. Traditionally, trabeculectomy was indicated following failed angle surgery. However, trabeculectomy surgery in children is especially challenging as it is less successful when compared to adults[12, 13] because of a vigorous healing response[14]. This has necessitated the use of adjunctive anti-scarring agents such as mitomycin-C (MMC) but at the cost of an increased risk of potentially serious complications such as hypotony and bleb related problems. [15-19] However even with MMC, the literature suggests disappointing outcomes for trabeculectomy in infants (especially less than one year of age) when compared to older children[15, 16, 18, 20] and also when compared to glaucoma drainage devices (GDD)[21]. GDD in children carry a significant risk of tube related problems such as tube-cornea touch in up to 26% cases[21-23] and tube migration or extrusion often necessitating the need for further tube related surgery

28   in up to a third of cases[3, 21]. Consequently, there is no consensus on the optimum surgery

29   following failed angle surgery[6].

30

31   Contemporary trabeculectomy techniques involving fornix-based conjunctival dissection,

32   releasable sutures and a wide area of anti-scarring application (a technique often described

33   as the Moorfields Safer Surgery System)[24, 25] have evolved over the past 15 years with the

34   aim of encouraging posterior aqueous flow and the development of diffuse drainage blebs.

35   These changes were developed to reduce the high incidence of sight threatening

36   complications, particularly bleb related problems, in children and subsequently applied to

37   adult surgery. [26, 27] The aim of this study was therefore to evaluate the long-term safety and

38   effectiveness of this surgical technique in infants undergoing trabeculectomy within the first

39   two years of life.

40

41   **Patients and Methods**

42   The protocol for this project was granted institutional review board approval by the Clinical

43   Audit Assessment Committee of Moorfields Eye Hospital. A retrospective case note review

44   was performed on the records of all children aged two years or younger that underwent

45   MMC augmented trabeculectomy by a single surgeon (MP) between May 2002 and

46   November 2012. Some children underwent sequential surgery to both eyes but no

47   simultaneous bilateral surgery was performed. In these situations, each individual eye was

48   regarded as a separate data entity for the purpose of analysis. All cases had a minimum of

49   12 months of follow up.

50

51   **Standard Surgical Technique**

52   The surgical procedure involved the creation of a superior fornix-based conjunctival peritomy

53   and a rectangular (5mm x 4mm) lamellar scleral flap with a crescent blade at the 12 o' clock

54   position. Due to the very elastic nature of the infantile sclera, only short radial cuts were

55 made which enabled tight closure without the need to suture the radial edge of the flap whilst

56 also encouraging posterior aqueous flow. A wide area of subconjunctival space

57 (approximately 3 clock hours) was then treated with MMC soaked Merocel corneal shields

58 (Beaver Visitec, UK), as was the undersurface of the scleral flap with a tear film strip (Sno-

59 strips, Chauvin Pharmaceuticals Limited, UK) cut to size. MMC was applied at

60 concentrations varying between 0.1-0.5mg/ml (at surgeon's discretion dependent upon risk

61 factors for failure) for 3 minutes before irrigation with 20ml of balanced salt solution. 10-0

62 nylon (Alcon, UK) was used to preplace intralamellar scleral sutures, with a fixed suture at

63 each corner and two releasable sutures at the posterior edge of the scleral flap. Following

64 insertion of an anterior chamber (AC) maintainer (Lewicky, Beaver Visitec UK), the AC was

65 entered at the anterior edge of the scleral bed. A 500μm sclerostomy was created with a

66 Khaw Descemet membrane punch 7-101 (Duckworth & Kent, UK) followed by a surgical

67 iridectomy. Further sutures were placed in the scleral flap, as required, with the aim of

68 achieving no aqueous flow through the flap at the end of procedure. Tenonectomy was not

69 performed. The conjunctiva was closed with 10-0 nylon sutures and in most cases a small

70 volume of viscoelastic (usually Provisc® (Alcon, UK)) and sterile air were injected into the

71 AC. Subconjunctival injections of steroid (Betamethasone) and antibiotic (Cefuroxime) were

72 given at the end of the case. All eyes were patched overnight.

73

74 Postoperatively, all patients received daily intensive steroid drops (dexamethasone 0.1%)

75 every 2-3 hours and ointment at night (Maxitrol – dexamethasone, neomycin sulfate and

76 polymyxin b sulfate ointment). Topical steroids were gradually weaned over 3-5 months as

77 dictated by the degree of conjunctival inflammation. Antibiotic drops (Chloramphenicol) four

78 times a day were usually stopped within 2-3 weeks of surgery once all exposed sutures were

79 removed. Cycloplegics were not routinely administered. Parents were advised to tape a

80 plastic shield over the operated eye at night time for the first month after surgery.

81

82 **Postoperative Management**

83   All children were examined at 1 day, 1 week, three weeks and six weeks after surgery, with

84   subsequent outpatient visits dependent upon clinical progress. Examination under Ketamine

85   anesthesia (EUA) took place at 1, 3 and 6 weeks after surgery when releasable sutures

86   were loosened or removed and subconjunctival steroid and/or 5-fluorouracil (5-FU) injections

87   (0.2-0.3ml of 50mg/ml solution) administered depending upon the characteristics of the bleb

88   and the degree of bleb inflammation. Measurements of corneal diameter and axial length

89   were also performed. Subsequently, additional glaucoma surgery was undertaken in eyes

90   uncontrolled by glaucoma medications.

91

92   Visual acuity, IOP, slit lamp biomicroscopy examining bleb morphology, anterior chamber

93   depth, wound status and lens clarity were routinely performed along with evaluation of the

94   optic nerve and retina at each postoperative visit. Quantitative visual acuity was measured

95   when the child's age and developmental abilities allowed. IOP measurements were obtained

96   using either Perkins applanation tonometry under Ketamine anesthesia, rebound tonometry

97   (Icare, Finland) or Goldmann applanation tonometry as the children became older.

98   Amblyopia was appropriately treated with refractive correction and a patching regime.

99

100   **Outcome Measures**

101   Surgical success was defined as IOP≤21mmHg and ≥5mmHg either with (qualified success)

102   or without (complete success) topical glaucoma medications, no further glaucoma surgery

103   (including bleb needling which was considered a failure), no devastating complications or the

104   loss of light perception vision and stable ocular dimensions (axial length, corneal diameter)

105   and optic disc cupping. Manipulation of the scleral flap (bleb massage), removal/adjustment

106   of releasable sutures were not considered as criteria for failure, as these comprise routine

107   post-surgical care with the technique employed. Complications and details of postoperative

108   interventions following the initial trabeculectomy were noted.

109

110   **Statistical Methods**

7

111   Data analysis was performed using Graphpad Prism (Graphpad, USA). Demographic data

112   were reported as the mean ± standard error with the range specified. Surgical success was

113   evaluated by Kaplan-Meier life-table analysis. Survival curves between subgroups were

114   compared using the log-rank (Mantel-Cox) test with Chi-Squared significance test.

115   Parameters between the groups designated success and failure were compared using either

116   a two-tailed unpaired t-test with Welch's correction or else by a Mann-Whitney Test,

117   depending on whether the populations fitted a Gaussian distribution as shown by the

118   D'Agostino & Pearson normality test. Retrospective contingency table analysis was

119   performed using a two-tailed Fishers Exact Test. Statistical significance was considered for

120   values at $p<0.05$.

121

Results

Patient Demographics and Preoperative Clinical Status

124   Forty consecutive eyes of twenty-six children were identified as having undergone MMC

125   augmented trabeculectomy before two years of age within the designated study period. The

126   full patient record was available for all the cases identified and the baseline demographic

127   data of the group studied are summarized in Table 1. Children ranged in age from 1 to 19

128   months with a mean of 9.0 ± 0.8 months. All eyes were phakic and most had PCG that had

129   undergone previous angle surgery in the form of goniotomy with a mean of 1.1 ± 0.1

130   procedures. Three eyes with PCG due to corneal edema and four eyes with secondary

131   childhood glaucoma (2, AR anomaly and 2 aniridia) did not have goniotomies. Forty-one

132   percent of infants with PCG had goniotomy repeated when the first goniotomy had reduced

133   the IOP but to an unsatisfactory level. None of the secondary glaucoma cases had angle

134   surgery repeated. The mean preoperative IOP was 24.2 ± 0.7 mmHg using an average of

135   2.1 ± 0.2 glaucoma medications, with no children receiving pre-operative acetazolamide.

136   The population was predominantly white but 23% were of black descent.

137

Surgical Procedure and Follow-up Period

There was a standard surgical approach in all cases as detailed above, with intraoperative MMC administered at a mean concentration of 0.22 ± 0.02 mg/ml (range, 0.1 – 0.5mg/ml). Eighty-three percent of cases had either 0.1-0.2 mg/ml concentration of MMC during surgery. Higher doses of MMC, ie. 0.5mg/ml, were used in children of Black or Middle Eastern descent only. The mean duration of follow up in successful cases was 72.9 ± 5.7 months (range, 26-129 months) and failure was observed at a mean of 29.0 ± 8.2 months (range, 1-90) .

Surgical outcomes

A summary of the postoperative care and outcomes at the final follow up for groups designated as success or failure is shown in Table 2.

Twenty-six of forty eyes (65.0%) were considered successful at the time of last follow up, of which 62.5% (25/40 cases) were regarded as a complete success and 2.5% (1/40 cases) a qualified success with the use of topical medication. The mean postoperative IOP at the last follow up visit for all successful eyes was 11.9 ± 0.7 mmHg with a mean reduction of 48.8% ± 4.0% from the preoperative baseline. Eyes classed as failures had a mean IOP of 23.4 ± 1.2 mmHg at the time of failure and achieved a mean final IOP of 14.5 ± 1.0 mmHg with a 38.4% ± 5.1% reduction from baseline after additional surgery. In addition to the IOP reading, glaucoma progression was determined by clinical signs and biometric parameters. Nine out of the fourteen failures had releasable sutures removed within the first 6 weeks and in seven this was also associated with needling. There was no significant difference between the dose of MMC, duration of postoperative topical steroids, the number of EUAs, 5-fluorouracil (5-FU) or steroid injections administered to those deemed successful and those considered failures.

165 Kaplan-Meier life-table analysis (Figure 1) demonstrated a mean cumulative probability of

166 success (95% confidence interval) at 6 months and 12 months (1 year) of 0.80 (0.64-0.89)

167 and 0.78 (0.61-0.88) respectively. The cumulative probabilities of success at 60 months (5

168 years) (modelled on 18 eyes) and at 87 months (7.3 years) (modelled on 9 eyes) after

169 surgery were 0.67 (0.49-0.80) and 0.60 (0.38-0.76) respectively. When analyzed according

170 to age at surgery, there was a trend towards greater success rates at the end of follow up

171 observed in those twelve months or younger (70.4%) compared to of those over twelve

172 months of age (53.8%). There was no difference in underlying diagnosis between the two

173 groups. Life-table analysis comparing outcomes of cases of primary congenital glaucoma to

174 those with secondary childhood glaucoma showed no significant difference in survival

175 between these etiologies over the course of follow up (Figure 2).

176

177 Data from all eyes (including 14 children with both eyes included in the study) were used for

178 analysis. There is potential for introducing bias by analyzing fellow eyes as independent

179 entities. In order to address this, we performed Cox Regression allowing for clustering,

180 which produced similar results to those found ignoring non independence. Of the 14 children

181 who had two eyes included in the study, failure was observed in both eyes in 2 children,

182 success was observed in both eyes in 5 children. The remaining children failed in one eye

183 but were successful in their fellow eye. A test for symmetry was conducted (p=0.7) indicating

184 little evidence of an association (albeit with low power). These observations would suggest

185 that our findings are robust to non-independence and justify the inclusion of data from all

186 eyes in the analyses presented.

187

188 Final visual acuity in all eyes studied was 0.69 ± 0.1 with 34.2% achieving the equivalent of

189 20/40 or better, 89.5% seeing 20/200 or better and with no cases of loss of light perception.

190 Almost half the children with successful outcomes had visual of acuity of 20/40 or better.

191

192 **Surgical Complications and Postoperative Interventions**

10

193 There were no recorded cases of hyphema, flat AC, early or late bleb leak, chronic

194 hypotony, endophthalmitis or retinal detachment observed in this series. Choroidal effusions

195 in the presence of a shallow AC and low IOP were observed in four cases (10%) with B-scan

196 ultrasound routinely performed at one week after surgery. Only one of the cases was with

197 the use of MMC 0.5mg/ml. Two cases resolved following intracameral viscoelastic injection,

198 one case did not resolve following intracameral viscoelastic injection and underwent re-

199 suturing of the scleral flap and the fourth resolved with conservative management. All four

200 cases went on to have a successful outcome.

201

202 Only one of the 40 eyes developed a cystic avascular bleb with all the other eyes being non-

203 cystic in nature (diffuse and elevated or flat). This specific case also suffered blebitis ten

204 years after trabeculectomy although it responded well to topical and systemic antibiotic

205 treatment alone with no change in IOP control or visual acuity. Diffuse, elevated bleb

206 morphology was noted in 63% of eyes (25 eyes) and 35% (14 eyes) had a flat appearance,

207 of which 86% (12 eyes) were observed in eyes classes as failures.

208

209 The presence of cataract, usually a small posterior subcapsular cataract, was noted in 20%

210 (8/40) of all eyes across the study group. The presence of cataract was observed in 11.5%

211 (3/26) eyes) in the group deemed to be successful at the end of follow up at a mean of 33.7

212 ± 14.4 months after trabeculectomy surgery. None of these patients required cataract

213 surgery as their vision was not thought to have been significantly impacted by the cataract to

214 warrant surgery (one case had visual acuity of 0.1 and the other 2 cases were unchanged at

215 0.8 and 0.9). The majority of observed cataract formation (5/8 cases), including a single

216 case that required surgery, occurred in the failure group at a mean of 56.4 ± 10.5 months

217 after trabeculectomy surgery. In these cases, cataract development occurred after further

218 glaucoma surgeries in all cases (3 cases of needling followed by Baerveldt tube insertion, 1

11

219 case of needling followed by repeat trabeculectomy with MMC 0.5mg/ml adjacent to the

220 original, 1 case of needling followed by cyclodiode laser).

221

Reasons for Failure

223 Postoperative interventions across the study group are summarized in Table 3. The fourteen

224 eyes that failed all did so because of uncontrolled IOP requiring further intervention. All eyes

225 that were considered as failures, were due to bleb needling being performed. These were

226 performed at a mean 28.2 ± 7.5 months after trabeculectomy with an average of two

227 needlings performed per eye. Needling alone controlled the IOP in only 21.4% (3/14 eyes) of

228 cases. Ultimately, after failed needlings (11/14 eyes), eight eyes underwent Baerveldt

229 implant insertion, one eye underwent a repeat trabeculectomy with MMC 0.5 mg/ml, one eye

230 required cyclodiode laser treatment and one eye underwent cyclodiode laser followed by

231 Baerveldt implant insertion. There was a significant association with bleb needling and

232 further glaucoma surgery being performed (p<0.0001). However despite this group being

233 regarded as failures, they did achieve a mean final IOP of 14.5±1.0 mmHg with a mean 38.4

234 ± 5.1% reduction of IOP from baseline with no loss of light perception vision, indicating that

235 needling procedures and subsequent surgeries were largely successful in the restoration of

236 intraocular pressure control.

237

Discussion

239 Trabeculectomy has traditionally been the procedure of choice after failed angle surgery to

240 control IOP in children. But in contrast to adults, trabeculectomy surgery in children is

241 associated with poorer outcomes[12, 13] due to a more aggressive healing response[14] and the

242 potential challenges of reduced compliance and lack of co-operation with examination.

243 Nonetheless, success of MMC trabeculectomy in children has been reported to be 59-95%

244 (IOP ≤ 21mmHg) with short follow up of 2 years or less[15-18, 20, 28] reducing to 55% after 6

245 years mean follow up[29]. All these studies are retrospective which makes comparison difficult

246   as success is influenced potentially by a number of factors such as: definition of success,

247   patient's age and race, case mix (primary and secondary glaucomas), inclusion of non

248   phakic patients, previous surgery, surgical technique, dose and duration of MMC, use of 5-

249   FU post operatively and duration of follow up.

250

251   In a number of studies, infancy has been shown to be a significant risk factor for failure.

252   Reported outcomes of trabeculectomy in infants less than one year of age vary between 15-

253   43%[15, 16, 18, 20]. Beck *et al*[20] reported that being aged less than 1 year at the time of surgery

254   was associated with almost a six-fold risk of failure. For infants less than 2 years of age,

255   Beck *et al*[21] reported a cumulative success rate of 36% (IOP < 23mmHg with medications) in

256   24 eyes at 1 year which dropped to only 19% at 6 years in a group with both primary and

257   secondary childhood glaucoma which included aphakic and pseudophakic patients. In a

258   larger series, Al Hazmi *et al* described a success rate of 39% (IOP < 21mmHg without

259   topical medications) in 66 eyes (unreported follow up) in a study population mostly of PCG

260   patients from the Middle East[15].

261

262   In comparison, our long-term outcomes of trabeculectomy with MMC for glaucoma

263   presenting in infants less than 2 years of age are more encouraging, with a cumulative

264   probability of success at one and seven years of 78% and 60% respectively. Almost all

265   successful cases (25/26; 96%) were not using topical IOP lowering medications at final

266   follow up. In infants less than one year of age, 70% were successful at the end of follow up.

267

268   The significant difference in outcomes of our study compared to published reports may

269   relate to a number of factors. Our study group was predominantly white, PCG cases and

270   included no patients with aphakia /pseudophakia or previous surgery involving the

271   conjunctiva, both known to be significant risk factors for trabeculectomy failure[13, 20, 30-33].

272   The pre-operative IOP in our series was lower than in comparable series which may have

273   contributed to improved outcomes. Furthermore surgical technique, namely MMC treatment

274   under the scleral flap also performed by other authors[15, 18] and close post-operative

275   management with further subconjunctival 5-FU and steroid may have also played a role. It is

276   likely the intensive post-operative bleb management achieved early diffuse posterior

277   aqueous flow, which contributed to successful long-term outcomes. Although it could be

278   argued that a significant number of EUAs were necessary, this has to be seen within the

279   context of overall results and that in successful cases (65%) one operation was all that was

280   necessary to achieve glaucoma stability over the duration of follow up. In comparison, Taylor

281   and colleagues[1] describe children with PCG (117 patients) requiring on average of 4.3 ± 3.8

282   (range 0-23) operations over a 20 year observation period to manage their glaucoma.

283

284   Trabeculectomy surgery in young children has fallen out of favor not only because of

285   reported poor outcomes but also because of the association with significant surgical

286   complications including flat anterior chambers (10%), choroidal effusions (22%),

287   suprachoroidal hemorrhage, retinal detachments and phthisis[18, 20]. In particular, thin

288   avascular, cystic blebs commonly occurred,[16,18] predisposing to bleb related infection such

289   as endophthalmitis (5-8%)[20, 29],and chronic late, bleb leaks (23%)[16]. As a consequence,

290   contemporary pediatric trabeculectomy techniques have evolved in recent years from those

291   used by comparative papers (e.g. limbus-based conjunctival flap and fixed sutures) with the

292   aim of reducing the burden of complications.[24, 25,27] All cases in this series were performed

293   using a standardized technique based on the Moorfields Safer Surgery System [24, 25] aimed at

294   achieving posteriorly directed aqueous flow. Specific modifications for pediatric

295   trabeculectomies include limited radial cuts to avoid anterior limbal flow and excessive flow

296   through the flap, MMC treatment under the scleral flap as well as the subconjunctival tissue

297   and the use of an AC maintainer in all cases.

298

299   In our study the commonest early complication was choroidal effusion at one week after

300   surgery in 10% (4/40 eyes), which is lower than the published literature which ranges from

301   17-23%.[16, 20, 21] Susanna *et al.*[18] reported a 5% rate of choroidal detachment but suspected it

302   was higher some eyes with shallow anterior chambers were not fully dilated when examined.

303   Our observed rate of cataract development in the cohort with successful outcome (11.5% -

304   none requiring surgery) was comparable to the existing literature for the same duration of

305   follow up[21].

306

307   The accepted alternative to trabeculectomy following failed angle surgery is the insertion of a

308   glaucoma drainage device (GDD). Only a few studies specifically evaluate the performance

309   of GDD in the infant population. Success rates at one year are reported at 74-87%[21, 34] with

310   53% survival at 6 years after surgery[21]. Our trabeculectomy outcomes are comparable

311   although direct comparison is difficult due to the presence of aphakic glaucoma cases in

312   these populations. However the major difference between our findings and those reported

313   following tube surgery is the significant associated complications often requiring surgical

314   revision. Beck et al reported 45.7% of eyes with a GDD required one or more operations due

315   to a complication related to the implant (most commonly tube corneal touch and exposure),

316   in contrast to 12.5% of eyes in trabeculectomy group[21]. Tube malposition, erosion and

317   endophthalmitis are consistently reported with greater frequency in the pediatric compared

318   to adult population [3]. Tube malposition requiring further surgery has been reported in 26-

319   35% of cases[21, 34]. These studies also reported corneal decompensation (9%), vitreous

320   hemorrhage (7%), endophthalmitis (7%) and retinal detachment (7%) following GDD

321   surgery. Overall, complications in our series were fewer than reported in comparable

322   literature following trabeculectomy and glaucoma drainage device surgery. This is important

323   as the technique is simple and does not require expensive special equipment. Furthermore

324   of significance, the need for medications appears to be higher following GDD compared to

325   trabeculectomy.[20] In one study, only 14% of infants undergoing GDD surgery achieved IOP

326   control without topical medications[34] compared to 62.5% (25/40) of our trabeculectomy

327   cases.

328

329 Criteria for success in glaucoma are largely based on IOP related parameters and the

330 absence of serious complications. However, the preservation of visual function is the goal in

331 these children and is influenced by factors other than IOP, such as corneal clarity, refractive

332 status and amblyopia which must also be addressed. In our study, final overall visual acuity

333 outcomes of 34.2% seeing 20/40 or better, 89.5% seeing 20/200 or better and no cases of

334 loss of light perception were very encouraging and comparable to other published reports.[35]

335

336 This study is limited by the retrospective nature of the analysis and with the study population

337 comprising predominantly cases of primary congenital glaucoma. A randomized, multicentre

338 trial comparing MMC trabeculectomy and GDD would be of interest, as would a study on the

339 optimal MMC application method, concentration and duration.

340

341 In conclusion, this study demonstrates that MMC augmented trabeculectomy using simple

342 contemporary trabeculectomy techniques is an effective option in the management of

343 glaucoma within the first two years of life, as shown by the successful long-term outcomes

344 and low incidence of sight threatening complications. After failed goniotomy surgery or as

345 primary surgery for phakic secondary childhood glaucoma cases, trabeculectomy may offer

346 an infant with glaucoma an excellent opportunity to achieve long-term control of intraocular

347 pressure off medications and optimal visual outcomes. The close post-operative monitoring

348 and need for regular EUA required to achieve these results in comparison to GDD surgery is

349 balanced by the significantly lower surgical re-intervention rate and dependence on

350 medication for IOP control. Should failure occur later in life, the opportunity for GDD still

351 exists and the potential complications of such surgery will be delayed, perhaps beyond the

352 more critical period of visual maturation.

353

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355

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Tables and Figures

Table 1. Baseline Demographic Information

Patients	26
Eyes	40
Age (range (mean ± SE))	1 – 19 months (9.0 ± 0.8 months)
Number of previous goniotomies (mean, SE)	1.1 ± 0.1
Diagnosis (n, %)	
Primary Congenital Glaucoma	32 (80%)
Axenfeld-Rieger Anomaly	4 (10%)
Aniridia	2 (5%)
Naevus of Ota	1 (2.5%)
Cutis Marmorata Telangectasia	1 (2.5%)
Ethnicity/Race (n, %)	
White	26 (65%)
Black	9 (22.5%)
Asian	3 (7.5%)
Middle Eastern	1 (2.5%)
Mixed	1 (2.5%)
Number of topical pre-operative medications (mean, SE)	2.1 ± 0.2
Pre-operative IOP (mean, SE)	24.2mmHg ± 0.7

SE= standard error
IOP= intraocular pressure

Table 2. Summary of Final Follow up

	Total	Success	Failure
Eyes	40	26 (65%)	14 (35%)
Time to final follow up (months)	62.8 ± 5.7 (Range 1-129)	72.9 ± 5.7 (Range 26-129)	29.0 ± 8.2 (†***) (Range 1-90)
Mean concentration of MMC (mg/ml)	0.22 (range 0.1-0.5)	0.22 (range 0.1-0.5)	0.23 (range 0.1-0.5)
Number of EUAs	3.6 ± 0.2	3.5 ±0.2	3.9 ± 0.3
Number of Needlings	0.7 ± 0.2	0	1.9 ± 0.2(†**)
Releasable Sutures Removed/Adjusted	11/40 (27.5%)	2/26 (7.7%)	9/14 (64.3%)
Number of Steroid Injections	2.0 ± 0.2	1.8 ± 0.2	2.5 ± 0.4
Number of 5-FU injections	2.1 ± 0.2	1.8 ± 0.2	2.6 ± 0.4
Duration of postoperative topical steroids (months)	3.2 ± 0.3	3.1 ± 0.3	3.4 ± 0.5
IOP at Failure (mmHg)			23.4 ± 1.2
Final IOP (mmHg)	12.8 ± 0.6	11.9 ± 0.7	14.5 ± 1.0 (‡*)
Mean % IOP Reduction from Baseline	45.2% ± 3.2	48.8% ± 4.0	38.4% ± 5.1(†*)
Final VA (logMAR)	0.69 ± 0.1	0.41 ± 0.1	1.2 ± 0.3 (†**)
20/40 or better	34.2% (13/38)	44.0% (11/25)	15.4% (2/13)
20/200 or better	89.5% (34/38)	92.0% (23/25)	69.2% (9/13)

456
457 Data shown as mean ± standard error
458

459 **Table 2**. Summary of data at final follow up denoting observations of the total sample (40

460 eyes), eyes classified as having successful outcomes and eyes classified as failure. The

461 populations of successful eyes and those classified a failure were tested for normality using

462 the D'Agostino & Pearson normality test and compared with a two-tailed unpaired t-test with

463 Welch's correction (‡) if normality was shown else with a Mann-Whitney test (†). Observed

464 significant differences are indicated in the table (*** $p<0.0004$; ** $p<0.0032$; * $p<0.04$).

465 (EUA = Examination under anesthesia; 5-FU = 5-Fluorouracil; MMC = Mitomycin-C; VA =

466 visual acuity; IOP = intraocular pressure)

Table 3. Post-operative Surgical Interventions	
Scleral flap resuture	1/40 (2.5%)
Bleb needling	12/40 (30.0%)
Repeat Trabeculectomy	1/40 (2.5%)
Cyclodiode Laser	2/40 (5.0%)
Aqueous Shunt Insertion	9/40 (22.5%)

Table 3. Summary of postoperative procedures performed across all eyes during the follow up period. A single case of ear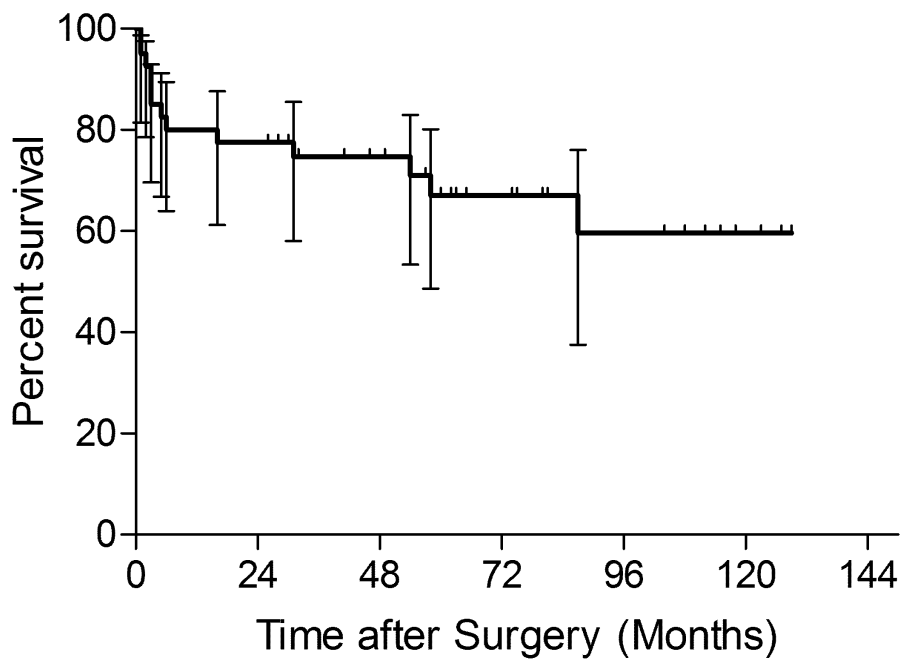ly hypotony unresponsive to an anterior chamber injection of viscoelastic required scleral flap re-suture and went on to be a success.
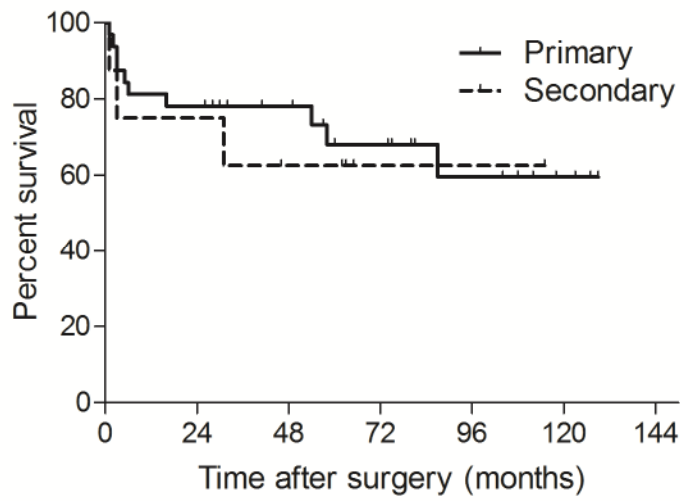
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481 **Figure 1.** Cumulative surgical success after Mitomycin augmented trabeculectomy in infants

482 by Kaplan-Meier life-table analysis. Plotted is the probability of success vs follow-up time

483 (error bars represent the 95% confidence interval). Mean cumulative probabilities of success

484 (95% confidence interval) at 6 months and 12 months (1 year) were 0.80 (0.64-0.89) and

485 0.78 (0.61– 0.88) respectively. The cumulative probabilities of success at 60 months (5

486 years) and at 87 months (7.3 years) after surgery were 0.67 (0.49–0.80) and 0.60 (0.38–

487 0.76) respectively.

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491 **Figure 2.** Cumulative surgical success by etiology after Mitomycin augmented

492 trabeculectomy in infants by Kaplan-Meier life-table analysis. Plotted is the probability of

493 success vs follow-up time for primary congenital glaucoma (solid line) and secondary

494 glaucomas (dotted line). The two curves were not significantly different when compared

495 using the log-rank (Mantel-Cox) test.

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