

Effect of use of mitomycin C on the outcome of Choanal atresia repair

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ABSTRACT

Objective: To investigate the effectiveness of topical mitomycin C (MMC) on outcome of endoscopic repair of choanal atresia (CA) in cases that had never had this operation and when nasal stent was not used.

Methods: Endoscopic repair of CA was performed in 20 children at King Abdul-Aziz University Hospital, Riyadh, Kingdom of Saudi Arabia between January 1999 and October 2005. Intra-operative application of topical MMC (0.4 mg/mL for 4 minutes) was carried out in 13 children, and 7 children did not receive MMC. The follow-up period ranged between 9 months and 6 years. The association between the 2 categorical variables was investigated using Fisher's exact test.

Results: Sixty-nine percent of the cases receiving MMC had a successful outcome compared with 57% of non-MMC cases, however, the difference was not statistically significant ($p=0.230$). In unilateral CA, 70% of those who received MMC had a successful outcome compared with 60% of those who did not; again the difference was not statistically significant ($p=0.566$). Successful outcome was considered when the posterior choana was patent during the successive follow up, without the need for revision surgeries.

Conclusion: We did not demonstrate a statistically significant difference between the percentages of children treated with MMC versus no-MMC who remained patent after surgery.

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Congenital choanal atresia (CA) is an uncommon anomaly that is reported in 1 in 5000-8000 births.^{1,2} It was first described by Roederer in 1755.^{3,4} This anomaly is more commonly encountered in females, with an estimated female to male ratio ranging between 1.6:1 and 2:1.^{1,2,4} Isolated CA may be seen more frequently, however, an association with other congenital anomalies can be seen in 20-50% of cases.^{1,2} The finding of CA should prompt a search for other congenital anomalies such as CHARGE association (ocular colobomas, heart defects, choanal atresia, retarded growth and central nervous system issues, genitourinary hypoplasia, and ear anomalies).² Unilateral CA is reported to be twice as common as bilateral CA.¹ Bilateral CA is commonly discovered immediately after birth with obvious upper airway obstruction, necessitating emergency management with either oropharyngeal airway, McGovern nipple, or intubation, until surgical repair of the CA is performed.¹ Unilateral CA, however, usually presents with less acute features, such as unilateral nasal obstruction and discharge, which commonly manifests latter in life. Opening of the posterior choana is the procedure to establish normal nasal breathing in cases of CA. Many approaches have been used including the transpalatal, transnasal, transantral, and trans-septal route.⁵ However, repair of CA by the endoscopic technique has become very popular in recent years. This can safely correct the difficult anatomical areas that have caused high failure rates in the past, namely, the lateral bony narrowing and the posterior septum.⁴ The outcome of endoscopic repair, however, is variable based on different studies.⁶⁻¹² Search for tools to improve outcome is very extensive.¹³ Topical mitomycin C (MMC) was introduced previously in an attempt to improve outcome and to maintain patent posterior choana. However, most of the studies in the literature using topical MMC are applying this drug to cases undergoing revision surgeries and cases with the use of a nasal stent. Therefore, it becomes difficult to evaluate the effectiveness of MMC in the presence of these confounding factors. The present study was undertaken to evaluate the effect of the application of

MMC without the use of nasal stent during endoscopic repair of CA in cases with no previous history of choanal surgery.

Methods. Thirty-seven consecutive children with the diagnosis of congenital choanal atresia were managed at King Abdul-Aziz University Hospital, Riyadh, Kingdom of Saudi Arabia between January 1999 and October 2005. We excluded from this study, cases with a history of prior attempt to open or dilate the posterior choana (5 children), children who were operated and endonasal stent was used (6 children), not operated upon because of medical reasons (2 children), and operated with Nd: YAG laser (one child). Twenty-three children fulfilled our selection criteria, none of them had prior surgical intervention, all underwent endoscopic repair of CA, and none of them had nasal stent post operatively. The cases were distributed randomly in an alternating way into one of 2 groups. The first group of children had an intraoperative application of topical MMC (0.4 mg/mL) to the dilated area by cotton pledget for 4 minutes. Followed by irrigation with 15cc of saline to the site of application. This group included 13 children. In the second group, no MMC was used. This group included 10 children. Unfortunately 3 cases were lost to follow up in this group. Endoscopic repair of CA was performed utilizing 0o telescope (2.7 or 4 mm) connected to a camera and a monitor. Opening of the soft tissue and dilatation was performed utilizing microdebrider. A microdebrider drill or skeeter drill was used to dilate the bony atresia laterally and to resect the posterior margin of the septum along with backbiting forceps. All our cases received saline nasal wash for one month after surgical intervention. Criteria for successful outcome included all the following; size of the posterior choana of at least 4 mm in diameter by fiberoptic examination, absence of symptoms of nasal obstruction or discharge, and lack of the need for further intervention or dilatation. Follow-up of our patients ranged between 9 months and 6 years with a mean follow up period of about 32 months.

Fisher's exact test was used to compare categorical variables. A *p*-value of less than 0.05 indicated statistical significance. For all statistical test, we used the Statistical Package for Social Sciences version 11.5 software.

Results. A total of 20 children were included our study. Their age ranged between 11 days and 17 years, with a mean of 7.9 years. Eight of our patients were boys and 12 were girls. Five cases had bilateral CA, and 15 cases had unilateral CA. All our cases had mixed bony and membranous atresia, except one who had bony atresia only. Nine cases (69%) of the MMC group had successful outcome compared to 4 cases (57%) of the children in the non-MMC group. however, this

difference was not statistically significant ($p=0.230$). In this study 15 of the cases had unilateral CA, 10 received MMC and 5 did not receive it. Seventy percent of those who received MMC had successful outcome compared to 60% of those who did not. Statistically there was no significant difference between the 2 results ($p=0.566$). A total of 5 cases had bilateral CA, 3 MMC. Sixty-seven percent of those who received MMC had successful outcome compared to 50% of those who did not. This difference was not statistically significant ($p=0.700$). Seventy percent of the unilateral CA receiving MMC had successful outcome compared to 67% of the bilateral cases. Statistically there was no significant difference between the 2 results ($p=0.706$). Isolated CA was seen in 13 cases. However, 7 of the cases were associated with other congenital anomalies including; CHARGE, Treacher Collins syndrome, Down syndrome, Apert syndrome, isolated cardiac, renal, and ear anomalies. Forty percent of the cases with associated other anomalies had successful outcome compared to 50% of the cases without associated anomalies. This difference was not statistically significant ($p=0.58$).

Discussion. Mitomycin C is an aminoglycoside antibiotic made by the fungus *Streptomyces caespitosus*.⁶ It acts by inhibiting DNA synthesis and breaking DNA strands. It is a drug that has long been used as an antineoplastic agent.¹⁴ Because of the inhibitory effect of this drug on fibroblast proliferation and migration, it is successfully used to maintain trabecular patency in glaucoma surgeries,¹⁵ and preventing scarring and maintain patency in laryngeal surgeries.¹² The use of MMC as an adjunct to surgical repair of CA was introduced earlier, with studies indicating favorable outcome.^{6,7,16} Prasad et al,⁶ in their review of 20 children who underwent endoscopic repair of CA and application of MMC (0.5mg/mL) for 3 minutes, reported a success rate of 85%. However, in 40% of their patients surgical intervention and use of MMC had to be repeated twice and 60% of their patients were revision cases. Bradford et al,¹⁶ compared cases that had MMC (0.4 mg/mL) for 3 minutes at the time of surgical repair of CA to historical controls for which MMC was not used. They reported a success rate of approximately 60% in the MMC group compared to 7% in the control group. The use of MMC in airway surgeries may precipitate early obstruction because of delayed wound healing with formation of sloughs, debris, or cartilage collapse of unhealed cartilage.¹⁷ Kubba et al,¹⁸ did not notice any significant difference in outcome of repair of choanal atresia for those who received MMC and those who did not. However, they used a smaller dose of topical MMC and shorter application time (0.2 mg/mL for 2 minutes).

Also there was variability in the time of use of MMC in the post-operative period, and their data was limited by random use of steroids and KTP laser for some of the patients. In our study, the decision was made at the beginning to use topical MMC in a higher concentration (0.4 mg/mL) and longer application time of 4 minutes compared to the concentration and duration used in Kubba's study. Our results, however, did not show a major difference in outcome between those who received MMC (success rate 69%) and those who did not receive it (success rate 57%). This difference was not statistically significant ($p=0.230$). When comparing the outcome of unilateral to bilateral cases receiving MMC, we found that the success rate in unilateral cases was 70% and in bilateral cases was 67%, which was not a statistically significant difference ($p=0.706$). The number of bilateral cases, however, was small in our study, which may have affected this result. An attempt was also made in this study to assess the effect of use of MMC among the unilateral cases. Seventy percent of the unilateral cases receiving MMC had a successful outcome, and 60% of the unilateral cases not receiving MMC had a successful outcome. Statistically, the difference in results was not significant ($p=0.566$). This indicated that there was no major benefit in the use of MMC in unilateral cases. This is not in agreement with the results of Rombaux et al.¹⁰ They indicated patent posterior choana with the use of MMC in unilateral CA in 85% of cases compared to 47% of cases without use of MMC. The use of MMC, however, lacks standardization, with no agreement on dose, period of application or frequency of application.^{6,7,16,18} Animal research suggests a higher dosage MMC may have more beneficial effects,¹⁹ which was also used in human studies.²⁰ This may represent the way to improve outcome of surgical intervention in case of CA. However, we still need further studies in this area. The presence of other anomalies did not seem to have a major effect on the outcome of intervention in our cases. This is in keeping with results from other studies.² There is no statistically detected difference between children with CHARGE association and other patients in the number of procedures needed for cure, or in the need for follow-up surgery.²

In order to get a pure effect of mitomycin in our study, we avoided the use of endonasal stent. The use of a stent may be associated with poor outcome due to local irritation, ulceration and infection.²¹ The recommendations of other studies range between, no use of nasal stents,^{8,11} to a variable period of stenting.^{9,22} Van Den et al,⁹ reported a success rate of endoscopic repair of CA in 80% of cases with a brief stenting for 2 days. The present study suffers from the drawback of being based on a small sample size of only 20 children. This shortcoming may be responsible for the failure to detect

a difference between the success rates for the 2 groups of children that were investigated. The study may be said to have had low statistical power, and this was inevitable due to the rarity of CA cases, and the inclusion of only cases with no prior surgical repair. Further research needs to be conducted using a larger series of cases in order to arrive at reliable conclusions about the efficacy of MMC as an adjunctive to endoscopic repair of CA. However, for an uncommon anomaly like CA, such a large-scale series may take too long to accomplish.

In conclusion, the results from our study did not demonstrate a statistically significant difference between the percentages of children treated with MMC versus no-MMC that remained patent after surgery.

References

- Gujrathi CS, Daniel SJ, James AL, Forte V. Management of bilateral choanal atresia in the neonate: an institutional review. *Int J Pediatr Otorhinolaryngol* 2004; 68: 399-407.
- Samadi DS, Shah UK, Handler SD. Choanal atresia: a twenty-year review of medical comorbidities and surgical outcomes. *Laryngoscope* 2003; 113: 254-258.
- Schwartz ML, Savetsky L. Choanal atresia: clinical features, surgical approach, and long-term follow-up. *Laryngoscope* 1986; 96: 1335-1339.
- Josephson GD, Vickery CL, Giles WC, Gross CW. Transnasal endoscopic repair of congenital choanal atresia: long-term results. *Arch Otolaryngol Head Neck Surg* 1998; 124: 537-540.
- Deutsch E, Kaufman M, Eilon A. Transnasal endoscopic management of choanal atresia. *Int J Pediatr Otorhinolaryngol* 1997; 40: 19-26. Review.
- Prasad M, Ward RE, April MM, Bent JP, Froehlich P. Topical mitomycin as an adjunct to choanal atresia repair. *Arch Otolaryngol Head Neck Surg* 2002; 128: 398-400.
- McLeod IK, Brooks DB, Mair EA. Revision choanal atresia repair. *Int J Ped Otolaryngol* 2003; 67: 517-524.
- Schoem SR. Transnasal endoscopic repair of choanal atresia: Why stent? *Otolaryngol Head Neck Surg* 2004; 131: 362-366.
- Van Den Abbeele T, Francois M, Narcy P. Transnasal endoscopic treatment of choanal atresia without prolonged stenting. *Arch Otolaryngol Head Neck Surg* 2002; 128: 936-940.
- Rombaux P, de Toeuf C, Hamoir M, Eloy P, Bertrand B, Veykemans F. Transnasal repair of unilateral choanal atresia. *Rhinology* 2003; 41: 31-36.
- Holzmann D, Ruckstuhl M. Unilateral choanal atresia: surgical technique and long-term results. *J Laryngol Otol* 2002; 116: 601-604.
- Eliashar R, Eliachar I, Esclamado R, Gramlich T, Strome M. Can topical mitomycin prevent laryngotracheal stenosis? *Laryngoscope* 1999; 109: 1594-1600.
- Tzifa KT, Skinner DW. Endoscopic repair of unilateral choanal atresia with KTP laser: A one stage procedure. *J Laryngol Otol* 2001; 115: 286-288.
- Jassir D, Buchman CA, Gomez-Marin O. Safety and efficacy of topical mitomycin C in myringotomy patency. *Otolaryngol Head Neck Surg* 2001; 124: 368-373.
- Daniels JT, Occleston NL, Crowston JG, Khaw PT. Effects of antimetabolite induced cellular growth arrest on fibroblast-interactions. *Exp Eye Res* 1999; 69: 117-127.

16. Holland BW, McGuirt WF. Surgical Management of Choanal Atresia Improved Outcome Using Mitomycin. *Arch Otolaryngol Head Neck Surg* 2001; 127: 1375-1380.
17. Roh JL, Lee YW, Park CI. Can mitomycin C really prevent airway stenosis? *Laryngoscope* 2006; 116: 440-445.
18. Kubba H, Bennett A, Bailey CM. An update on choanal atresia surgery at Great Ormond Street Hospital for Children: preliminary results with Mitomycin C and the KTP laser. *Int J Ped Otolaryngol* 2004; 68: 939-945.
19. Ingrams DR, Volk MS, Biesman BS, et al. Sinus surgery: does mitomycin C reduce stenosis?. *Am Laryngol Rhinol Otol Soc* 1998; 108: 883-886.
20. Senders CW. Use of mitomycin C in the pediatric airway. *Curr Opin Otolaryngol Head Neck Surg* 2004; 12: 473-475.
21. Friedman NR, Mitchell RB, Bailey CM. Management and outcome of choanal atresia correction. *Int J Ped Otorhinolaryngol* 2000; 52: 45-51.
22. Singh B. Bilateral choanal atresia: key to success with the transnasal approach. *J Laryngol Otol* 1990; 104: 482-484.

Statistics

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