Effect of the type of surgery, use of intraoperative topical mitomycin C or stenting on the outcome of choanal atresia repair: a systematic review and meta-analysis

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Background
Restenosis and recurrence of symptoms after posterior choanal atresia (CA) repair is a major concern for surgeons, which leads to the use of a variety of surgical approaches and adjuvant treatment modalities to avoid restenosis.

Aim
The study was designed to compare the outcome of transnasal endoscopic and transpalatal repair of CA as regards restenosis, and also to compare the effect of using topical mitomycin C (MMC) or nasal stenting with not using these modalities on the outcome of repair as regards restenosis.

Methods
A systematic search was conducted on the PubMed/MEDLINE to locate and select relevant studies without applying any limits. Studies included in meta-analysis were tested for heterogeneity of the estimates.

Results
As regards comparing the transnasal endoscopic and transpalatal approaches, eight studies, involving 410 cases, met our criteria; 197 cases were repaired endoscopically with 37.5% restenosed and 188 through transpalatal approach with 28.2% restenosed. Using the estimated odds ratio, no statistically significant difference was found as regards restenosis. For the use of MMC, five articles fulfilled our criteria; they involved 155 cases; MMC was used in 70 cases where 24.2% restenosed, and was not used in 85 cases where 35.2% restenosed. By estimated odds ratio, there was no statistically significant difference between the two groups as regards restenosis. For the use of stenting, four articles fulfilled our criteria; they involved 165 cases, out of which 93 cases used nasal stent after repair of CA (21.5% restenosed), whereas in 72 cases stent was not used (18% restenosed). By estimated odds ratio there was no statistically significant difference between the two groups.

Conclusion
The available evidence suggests that there is no statistically significant difference between transnasal endoscopic and transpalatal approach in the repair of CA as regards restenosis; furthermore, there is no statistically significant difference between using intraoperative topical MMC and nasal stent and not using such modalities on the outcome of CA repair.

Keywords:
choanal atresia repair, mitomycin C, restenosis of choanal atresia repair, stenting, transnasal endoscopic, transpalatal

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Introduction
Choanal atresia (CA) is a relatively rare congenital anomaly occurring in about one in 5000–8000 live births; its female to male ratio is 2: 1. Generally, 65–75% of patients with CA are unilateral, and about 30% are pure bony, whereas 70% are mixed bony-membranous [1].

Management of these patients varies and depends on the type of atresia, age, and general condition of patients. The most common surgical techniques used are the transnasal and transpalatal approaches. While transnasal endoscopic approach is the method of choice and has been used successfully in newborns and infants and is suitable for membranous or very thin bony atresia, the transpalatal approach is normally reserved for the older children, thick bone, or cases with restenosis [2].
The concern was always to adequately repair CA and prevent recurrence of symptoms by preventing restenosis. Therefore, in this study we aimed to systematically review the data about the repair of CA and outcome of repair, through comparing, via statistical analysis, the transnasal endoscopic and transpalatal approaches as regards restenosis, and to find out the role of using mitomycin C (MMC) as adjuvant treatment and the role of stenting in improving the outcome of CA repair.

**Methods**

**Identification and location of articles**
Medline database at [http://www.pubmed.gov](http://www.pubmed.gov) was searched, using the keyword 'choanal atresia' without applying any limits. Then the search was conducted by entering the following keywords:

choanal atresia+repair, choanal atresia+endoscopic, choanal atresia+transnasal, choanal atresia+stent, and choanal atresia+topical mitomycin C. The last search was conducted on 10 January 2015.

**Screening and evaluation**

After blinding the articles regarding authors and journal of publication, the articles yielded by the search were screened regarding four inclusion and three exclusion criteria.

1. **Inclusion criteria**: Articles in which the number of cases reported was three or more in each group for case–control studies were included; in addition, only primary cases and those studies in which outcomes were reported in detail and complications mentioned were included in the present study.

2. **Exclusion criteria**: Review articles were excluded because there were no cases or results. Articles reporting on less than three cases or revision cases were also excluded. Only articles fulfilling the criteria of screening were included for further steps of data collection, analysis, and reporting.

**Data collection**

Data collected from the articles included the type of study, number of cases reported in each article, surgical approach used (whether transnasal endoscopic or transpalatal), and the topical application of MMC or stenting, functional outcomes (improvement of symptoms after treatment), and the presence and type of complications.

**Data analysis**

Statistical analysis was carried out using comprehensive meta-analysis, version 2 (Biostat, Englewood, New Jersey, USA). Every article fulfilling the criteria of screening and data collection was fed into the above-mentioned computer software.

**Testing for heterogeneity**

Studies included in meta-analysis were tested for heterogeneity of the estimates using the following tests:

1. Cochran Q chi square test: A statistically significant test ($P$-value $<0.1$) denoted heterogeneity among the studies.

2. $I^2$ index, which is interpreted as, $I^2=0–40%$: unimportant heterogeneity; 30–60%: moderate heterogeneity; 50–90%: substantial heterogeneity; and 75–100%: considerable heterogeneity.

3. $\tau^2$ index ($\tau^2>1$ = substantial heterogeneity).

**Pooling of estimates**

Risk for unwanted outcomes was expressed in terms of odds ratio with 95% confidence interval (CI); estimates from included studies were pooled using both the Mantel-Haenszel fixed-effects method and the DerSimonian laerd random-effects method.

**Examination of publication bias**

Publication bias was examined using the Funnel plot and Duval and Tweedie’s trim and fill tests.

**Results**

Searching Medline database, [http://www.pubmed.gov](http://www.pubmed.gov) with the last search on 10 January 2015 using ‘choanal atresia’ without applying any limits yielded 12 400 articles; the number of articles yielded by using each keyword is mentioned in Table 1.

**Results of comparing the outcome of transpalatal versus transnasal endoscopic repair of CA**

First, we compared between the studies of transnasal and transpalatal approach in CA repair. We screened for keywords choanal atresia, transnasal endoscope, and

| Search keywords | Number of articles |
|-----------------|-------------------|
| Choanal atresia | 12 400            |
| Choanal atresia+repair | 8010             |
| Choanal atresia+transnasal | 1320         |
| Choanal atresia+endoscopic | 3140    |
| Choanal atresia+stent | 1500             |
| Choanal atresia+mitomycin c | 396       |
transpalatal. We found eight articles fulfilling our criteria, and they involved 410 cases. Cases that were repaired endoscopically were 197 in number, whereas transpalatal approach was used in 188 cases. Restenosis occurred in 37.5% of those who had undergone endoscopic approach and in 28.2% of those who had undergone transpalatal approach (Table 2).

The incidence of restenosis after transnasal endoscopic or transpalatal repair, using the estimated odds ratio
(statistical measure), showed a statistically non significant difference between the two techniques. The measures of heterogeneity revealed unimportant heterogeneity of the estimates reported by the included studies (Cochran $Q$-value, 0.050; $I^2$, 50.318; $\tau^2$, 0.893). Pooling of the estimates using a fixed-effects model confirmed the result (pooled odds ratio, 1.58; 95% CI, 0.94–2.66), as shown in Table 3 and Figs. 1 and 2.

Moreover, the incidence of restenosis after transnasal endoscopic or transpalatal repair by using the estimated risk ratio (statistical measure) showed a statistically nonsignificant difference between the two techniques. Measures of heterogeneity revealed important heterogeneity of the estimates reported by the included studies (Cochran $Q$-value, 0.001; $I^2$, 72.740; $\tau^2$, 0.683). Pooling of the estimates using a random-effects model confirmed the result (pooled risk ratio, 1.25; 95% CI, 0.67–2.32), as shown in Table 4 and Fig. 3.

The funnel plot for the log risk ratio versus the SE of risk ratio showed some evidence of publication bias (Fig. 4). The Duval and Tweedie’s Trim and Fill method suggested that three studies were missing; under the random-effects model the point estimate and 95% CI for the combined studies was 1.25 (0.67–2.32); using Trim and Fill the imputed point estimate was 0.84 (0.44–1.57).

Results of comparing the outcome of transpalatal and transnasal endoscopic repair of CA with and without the usage of mitomycin C

When we screened the articles for the application of topical MMC for improving the outcome of CA repair by using key words choanal atresia and mitomycin C, seven articles met our criteria but two of them were excluded as these were one-armed studies giving insufficient data, and thus only five articles were included for comparison; these articles involved 155 cases, managed by transnasal endoscopic and transpalatal approach. MMC was used in 70 cases, and was not used in 85 cases. We found that the rate of restenosis in cases of MMC application was 24.28%.

### Table 3 Meta-analysis for the incidence of restenosis after transnasal or transpalatal repair using the estimated odds ratio as the effect measure

| Numbers | References            | Transnasal Events | Transpalatal Events | Total Events | Odds ratio | Lower limit | Upper limit | Z-value | P-value RW (F) | RW (R) |
|---------|-----------------------|-------------------|---------------------|--------------|------------|-------------|-------------|---------|----------------|--------|
| 1       | Al Muhaimeed [3]      | 10                | 24                  | 6            | 6          | 0.06        | 0.00        | 1.10    | −1.90           | 0.06   | 3.03       | 6.62   |
| 2       | Madry et al.[4]       | 19                | 45                  | 28           | 91         | 1.64        | 0.78        | 3.45    | 1.32            | 0.19   | 49.27      | 23.64   |
| 3       | Kim et al.[5]         | 9                 | 22                  | 7            | 12         | 0.49        | 0.12        | 2.06    | −0.97           | 0.33   | 13.24      | 16.21   |
| 4       | Gosepath et al.[6]    | 15                | 38                  | 0            | 3          | 4.62        | 0.22        | 95.73   | 0.99            | 0.32   | 2.94       | 6.46    |
| 5       | Hengerer et al.[7]    | 4                 | 23                  | 4            | 32         | 1.47        | 0.33        | 6.63    | 0.51            | 0.61   | 11.95      | 15.49   |
| 6       | Jung et al.[8]        | 7                 | 9                   | 6            | 30         | 14.00       | 2.30        | 85.40   | 2.86            | 0.00   | 8.26       | 12.87   |
| 7       | Richardson and Os Ruthorpe [9] | 9 | 25                  | 2            | 12         | 2.81        | 0.50        | 15.77   | 1.18            | 0.24   | 9.09       | 13.54   |
| 8       | Wiatrak [10]          | 1                 | 11                  | 0            | 2          | 0.71        | 0.02        | 23.31   | −0.19           | 0.85   | 2.22       | 5.18    |

**Model**

| Fixed | Random |
|-------|--------|
| 1.58  | 0.94   |
|       | 2.66   |
|       | 1.73   |
|       | 0.08   |
| 1.54  | 0.64   |
| 3.71  | 0.97   |
| 0.33  |        |

Tests of heterogeneity: Cochran $Q$-value = 0.050, $I^2$ = 50.318, $\tau^2$ = 0.893. Publication bias: Duval and Tweedie’s Trim and Fill number = 0. RW (F), relative weight under fixed model; RW (R), relative weight under random model.
whereas in cases without MMC it was 35.29% (Table 5).

The meta-analysis of studies comparing MMC application versus no MMC as regards the incidence of restenosis using the estimated odds ratio (statistical measure) showed a statistically nonsignificant difference between the two groups. Measures of heterogeneity revealed unimportant heterogeneity of the estimates reported by the included studies (Cochran Q P-value, 0.091; $I^2$, 50.1; $r^2$, 0.939).

Pooling of the estimates using a fixed-effects model showed an odds ratio of 0.643 (95% CI, 0.285–1.452; $P$-value, 0.288) (Fig. 5).

Results of comparing the outcome of transpalatal and transnasal endoscopic repair of CA with and without using stenting

For comparing the result of using nasal stent as an adjuvant tool to improve the outcome of transnasal or transpalatal approach, we screened for keywords choanal atresia and nasal stent. Seven articles met our criteria but three of them were excluded as these were one-armed studies giving insufficient data, and thus only four articles

| Numbers | References | Transnasal | Transpalatal | Odds ratio | Lower limit | Upper limit | z-value | P-value | RW (F) | RW (R) |
|---------|------------|------------|--------------|------------|-------------|------------|---------|---------|--------|--------|
| 1       | Al Muhaimeed [3] | 10 | 24 | 6 | 6 | 0.45 | 0.27 | 0.75 | −3.08 | 0.00 | 28.66 | 18.68 |
| 2       | Brodák-Moldý et al.[4] | 19 | 45 | 28 | 91 | 1.37 | 0.87 | 2.17 | 1.35 | 0.18 | 34.42 | 19.08 |
| 3       | Kim et al.[5] | 9 | 22 | 7 | 12 | 0.70 | 0.35 | 1.40 | −1.00 | 0.32 | 15.16 | 16.82 |
| 4       | Gosepath et al. [6] | 15 | 38 | 0 | 3 | 3.18 | 0.23 | 43.74 | 0.86 | 0.39 | 1.06 | 4.41 |
| 5       | Hengerer et al.[7] | 4 | 23 | 4 | 32 | 1.39 | 0.39 | 4.99 | 0.51 | 0.61 | 4.46 | 11.16 |
| 6       | Jung et al.[8] | 7 | 9 | 6 | 30 | 3.89 | 1.75 | 8.62 | 3.34 | 0.00 | 11.50 | 15.76 |
| 7       | Richardson et al. [9] | 9 | 25 | 2 | 12 | 2.16 | 0.55 | 8.49 | 1.10 | 0.27 | 3.89 | 10.43 |
| 8       | Wiatrak [10] | 1 | 11 | 0 | 2 | 0.75 | 0.04 | 14.19 | −0.19 | 0.85 | 0.84 | 3.66 |

Tests of heterogeneity: Cochran Q P-value = 0.001, $I^2$ = 72.740, $r^2$ = 0.683. Publication bias: Duval and Tweedie’s Trim and Fill number = 3. RW (F), relative weight under fixed model; RW (R), relative weight under random model.

Figure 3

Forest plot for the incidence of restenosis after transnasal or transpalatal repair using the estimated risk ratio (RR) as the effect measure. CI, confidence interval.

Figure 4

Funnel plot of the log risk ratio and the SE of risk ratio for determination of publication bias.

Figure 5

Showed the forest plot for meta-analysis of studies comparing mitomycin C versus no mitomycin C as regards the incidence of restenosis. CI, confidence interval.
were included; they involved 165 cases, managed by transnasal endoscopic and transpalatal approach. In total, 93 cases used nasal stent after the repair of CA, whereas in 72 cases stent was not used. Rate of restenosis in cases for which nasal stent was used was 21.5%, whereas in cases without nasal stent the rate of restenosis was 18% (Table 6).

Meta-analysis of studies comparing stent insertion versus no stent insertion after CA repair, as regards the incidence of restenosis using the estimated odds ratio (statistical measure), showed a statistically nonsignificant difference between the two modalities. The measures of heterogeneity revealed unimportant heterogeneity of the estimates reported by the included studies (Cochran $I^2$, 0.874; $Q$, 0.874; $I^2$, 0.000; $r^2$, 0.000).

Pooling of the estimates using a fixed-effects model showed an odds ratio of 1.427 (95% CI, 0.593–3.433; $P$-value, 0.428) (Fig. 6).

**Discussion**

Many surgical approaches have been described for CA repair; among them are the transnasal, transpalatal, trans-septal, and transantral routes. Although their success rate are almost equal, the most widely used techniques are the transnasal and transpalatal routes [18].

A study by Pirsig [19] reviewed over hundreds of papers on surgical approaches to CA. Many authors found that the results of both transnasal and transpalatal approaches are comparable (80 and 84% success rates, respectively).

This is in agreement with our study, as we found that the incidence of restenosis after transnasal endoscopic or transpalatal repair, using the estimated odds ratio and risk ratio (statistical measures), showed a statistically nonsignificant difference between the two techniques.

Whereas Shivakumar et al. [20], Panda et al. [21], Sadek [18], Reddy et al. [22], Wiatrak [10], Anderhuber and Stammberger [23], Forer et al. [24], Ibrahim et al. [25], Önerci et al. [26], Yaniv et al. [27], Friedman et al. [17], Romeh and Albirmawy [28], Van Den Abbeele et al. [29], Saetti et al. [30], Schoem [31] and Pasquini et al. [32], in their respective studies, preferred transnasal...
endoscopic approach, as it is quick, safe, and avoids hard palate and alveolar arch growth retardation, with less morbidity, and short hospital stay. In addition, it has the ability to exactly locate the site of puncture and drill the atretic plate under constant vision using the nasal endoscope.

On the other hand, a study by Bergonse et al. [33] reported that despite current development and improvement of endoscopic technique transpalatal technique, when performed properly by a skilled surgeon, the result is satisfactory. A study by Gujrathi et al. [34] suggested that endoscopic repair is difficult and should not be preferred in neonates because of narrow nasal cavities. Moreover, Schraff et al. [35] preferred transpalatal approach as the intervention of choice in CA repair.

During studying the results of meta-analysis of studies comparing MMC versus no MMC as regards the incidence of restenosis using the estimated odds ratio (statistical measure), we found that there was no statistically significant difference between using MMC or no MMC as regards the incidence of restenosis. In addition, a study by Teissier et al. [36] found that using topical MMC as an adjuvant treatment to CA repair does not improve the outcome. On the other hand, Prasad et al. [37], Holland and McGuirt [38], Bozkurt et al. [12], Rombaux et al. [14], Gosepath et al. [6], and Mcleod et al. [39] found that using topical MMC as an adjuvant treatment to CA repair has great effect in improving the outcome.

Finally, we aimed to find out the role of stenting in improving the outcome of CA repair.

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**Table 6 Articles involved in studying the role of Stenting in improving the outcome of repair of CA**

| References    | Methods                          | Participates                                                                 | Interventions                                      | Outcome                                                                 |
|---------------|----------------------------------|------------------------------------------------------------------------------|----------------------------------------------------|--------------------------------------------------------------------------|
| Elsherif et al.[16] | Prospective study                | 1. Study group with stent seven cases, five unilateral, two bilateral; Three male, four female; Age from 4 days to 17 years; Bony atresia in four cases, membranous in one case, mixed atresia in two cases; 2. Control group with no stent five cases, four unilateral, one bilateral; Two male, three female; Age from 2 days to 2 years; Bony atresia in three cases, membranous in one case, mixed atresia in one | Transnasal endoscopic repair                          | Three cases with nasal stent had restenosis; One case with no nasal stent had restenosis |
| Newman et al.[15] | Case–control (retrospектив study) | 42 cases, three of them were excluded because of inadequate follow-up data, excluding six patients whose initial repair was performed by other physicians; 19 unilateral, 12 bilateral; Age range from 3 days to 15 years; Bony atresia in six cases, membranous in three, mixed in 30 cases | Transnasal endoscopic approach in 31 cases; Transpalatal in two cases; Intranasal stents were used in 36 of 43 choanae (84%) operated on endoscopically. When we used stents, they were usually (in 28 of 36 patients) left in place for 15 days or longer | Five cases with nasal stent had restenosis; One case with no nasal stent had restenosis |
| Kubba et al.[13]  | Case–control (retrospектив study) | 46 cases; 23 unilateral (seven male, 16 female), 23 bilateral (nine male, 14 female); Type of atresia not mentioned | Transnasal endoscopic approach; Stent applied in 23 cases of bilateral atresia and in 10 cases in unilateral atresia; 11 cases lost in follow-up | Seven cases with nasal stent had restenosis; Two case with no nasal stent had restenosis |
| Friedman et al.[17] | Case–control (retrospектив study) | 65 cases; 30 unilateral, 35 bilateral; 19 male, 46 female; Type of atresia not mentioned | Transnasal endoscopic approach; Cases stented> 12 weeks, 5; Cases stented<12 weeks, 14 | Five cases with nasal stent had restenosis; Nine case with no nasal stent had restenosis |

CA, choanal atresia.

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**Figure 6**

**Stent vs. No Stent: Re-stenosis**

| Model | Odds ratio | 95% CI lower | 95% CI upper | p-value |
|-------|------------|--------------|--------------|---------|
| Elsherif et al. 2012 | 3.000 | 0.219 | 42.63 | 0.811 | 0.417 |
| Newman et al. 2013 | 0.076 | 0.085 | 0.724 | 0.328 | 0.740 |
| Kuebel et al. 2004 | 1.481 | 1.269 | 3.290 | 0.447 | 0.551 |
| Friedman et al. 2009 | 1.486 | 1.451 | 3.147 | 0.503 | 0.546 |
| Random | 1.427 | 1.503 | 3.430 | 0.703 | 0.420 |

Forest plot for meta-analysis of studies comparing stent insertion versus no stent insertion as regards the incidence of restenosis. CI, confidence interval.
The meta-analysis of studies comparing stent insertion versus no stent insertion as regards the incidence of restenosis using the estimated odds ratio (statistical measure) showed statistically nonsignificant difference between the two modalities.

Studies by Newman et al.[15], Kubba et al. [13], Friedman et al. [17], Cedin et al. [40], Gosepath et al. [6], Elloy [41], Durmaz et al. [42], and Uzomefuna et al. [43] agreed with our outcome that there is no statistically significant difference between using or not using stent as regards the incidence of restenosis.

Wiatrak [10] and Romeh and Albirnawy [28] found that using nasal stent as adjuvant tool to CA repair improves the outcome.

On the other hand, studies by Josephson et al.[44], Schoem [31], Van Den Abbeele et al. [29], Wang et al. [45], and Elsherif et al. [16] showed that the stents may act as a nidus for infection and cause pain, in addition to the formation of granulation tissue, and nasal synchia. Thus, using stent as an adjuvant tool to CA repair does not improve the outcome.

**Conclusion**

Although there is much debate about which approach is better and preferable in the repair of CA, the available evidence from this statistical analysis indicates that there is no statistically significant difference between transnasal endoscopic and transpalatal approach in the repair of CA as regards restenosis. In addition, we found that there is no statistically significant difference between using intraoperative topical MMC and nasal stent or not using such modalities in the outcome of CA repair.

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**Conflicts of interest**

There are no conflicts of interest.

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