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Amniotic Membrane Transplantation and Conjunctival Autograft Combined with Mitomycin C for the Management of Primary Pterygium: A Systematic Review and Meta-Analysis

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Outline

Introduction → Methods → Results → Discussion → Conclusion

Introduction

- **Pterygium** is an uncontrolled overgrowth of fibrovascular tissue that extends across the limbus and invades the cornea.[1]
- The pooled prevalence of pterygium is **10.2%**.[2]
- **Pterygium** causes astigmatism, recurrent inflammation, and obvious disfigurement.[1]
- The gold standard treatment for pterygium removal is **surgical excision with conjunctival autograft (CAG)** or **conjunctival limbal autograft**.[3]

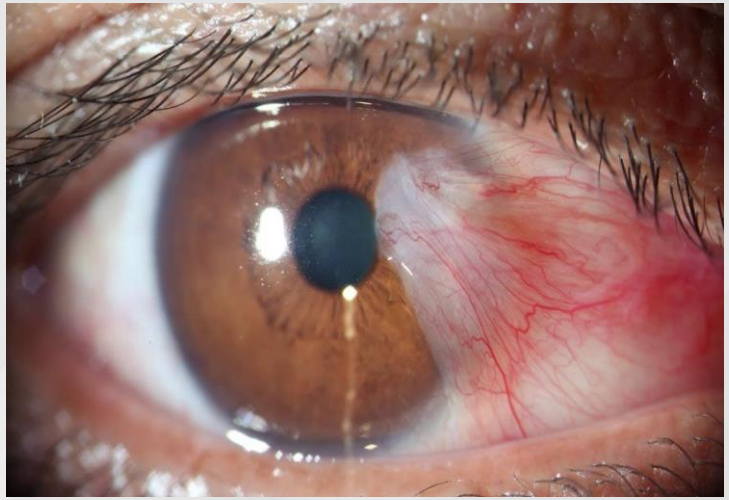

Figure 1: pterygium causing obvious disfigurement.

Introduction

❑ **Treatment:**

- Surgical excision with conjunctival autograft (CAG):
  - Risk of recurrence is 39%.[4]
- Surgical excision with amniotic membrane transplantation (AMT):
  - Risk of recurrence is 40.9%.[4]
- Surgical excision with CAG + mitomycin C (MMC):
  - Risk of recurrence is 9%.[4]

❑ The exact efficacy and safety of **MMC (antineoplastic antibiotic)** is unclear.

❑ Is it safe to combine **MMC** with **CAG** to ensure low risk of recurrence?

- Yes.[5,6]
- No.[7,8]

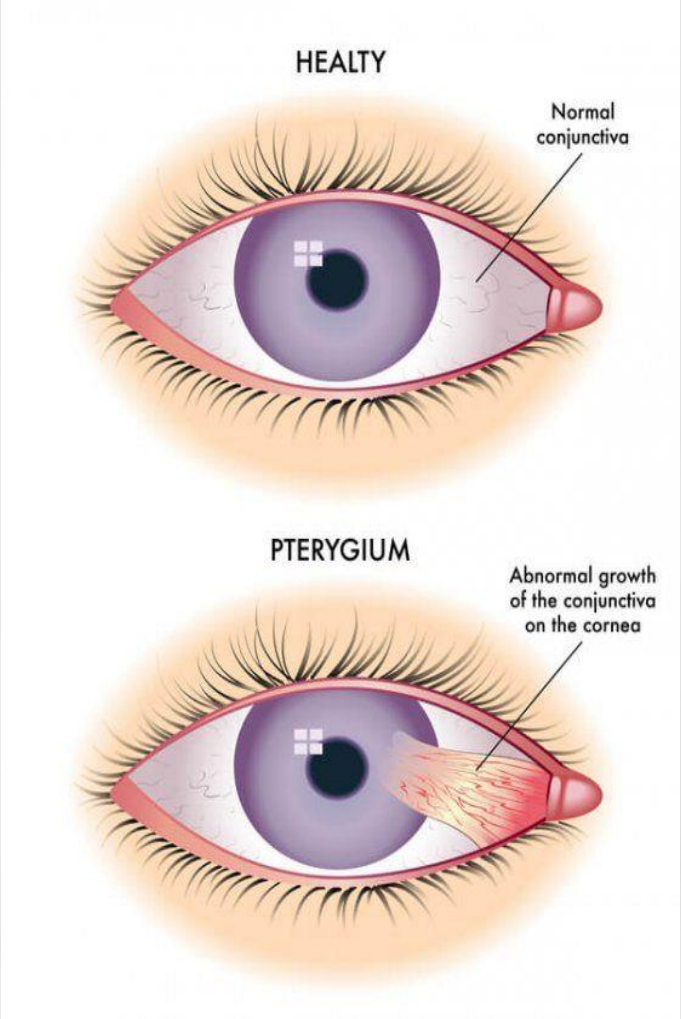

Figure 2: healthy eye (above) and eye with pterygium (below).

Introduction

❑Significance:

- Previous review was limited.
- Many RCTs were produced and reported opposite results.

❑ Aim:

- To examine the **efficacy** (recurrence rate) and **safety** (adverse events) of CAG combined with MMC or AMT compared to surgical excision with CAG alone for the treatment of primary pterygium.

CAG: conjunctival autograft
AMT: amniotic membrane transplantation
MMC: mitomycin C

Methods

❑Eligibility criteria:

Population	Participants who underwent surgical excision of primary pterygium.
Intervention	CAG+MMC, or AMT with or without MMC.
Comparison	CAG alone.
Outcome	1. Recurrence rate. 2. Adverse effects.
Study	RCTs.

Table 1: inclusion criteria

CAG: conjunctival autograft
AMT: amniotic membrane transplantation
MMC: mitomycin C

Methods

- This study is conducted according to a pre-specified protocol (CRD42022297725) and reported using PRISMA guidelines.

- Information sources and search strategy:
  - Databases: MEDLINE, EMBASE, CENTRAL.
  - Manual: Citations.
- Last search was on January 10, 2022.

Methods

❑Selection process

- ❑Two reviewers, independently, performed title and abstract screening against the eligibility criteria, full-text assessment.
- ❑Discrepancies were resolved through consensus or discussion with a third reviewer.

❑ Data extraction

- ❑Two reviewers, independently, performed data extraction from eligible trials.
- ❑Discrepancies were resolved through consensus or discussion with a third.

❑Quality assessment:

- **Risk of bias within studies:** The revised Risk of Bias 2 (RoB 2) tool.
- **Publication bias:** Visual inspection of the funnel plot.
- **Certainty of evidence:** GRADE criteria.

Methods

❑Meta-analysis:

- Random-effects model.
- Significance level: 95% with P-value <0.05 as a threshold.
- Effect measures: risk ratios.
- Heterogeneity: I2 for heterogeneity.

❑Subgroup analysis:

- CAG+MMC vs CAG alone.
- AMT vs CAG alone.

CAG: conjunctival autograft
AMT: amniotic membrane transplantation
MMC: mitomycin C

Results: study characterstics

- Number of studies: 12 studies.
- Total number of participants: 1144 patients.
- Intervention:
  - CAG alone: 557 patients.
  - CAG+MMC: 67 patients.
  - AMT: 520 patients.
- Mean participant's age: 40-60 years.

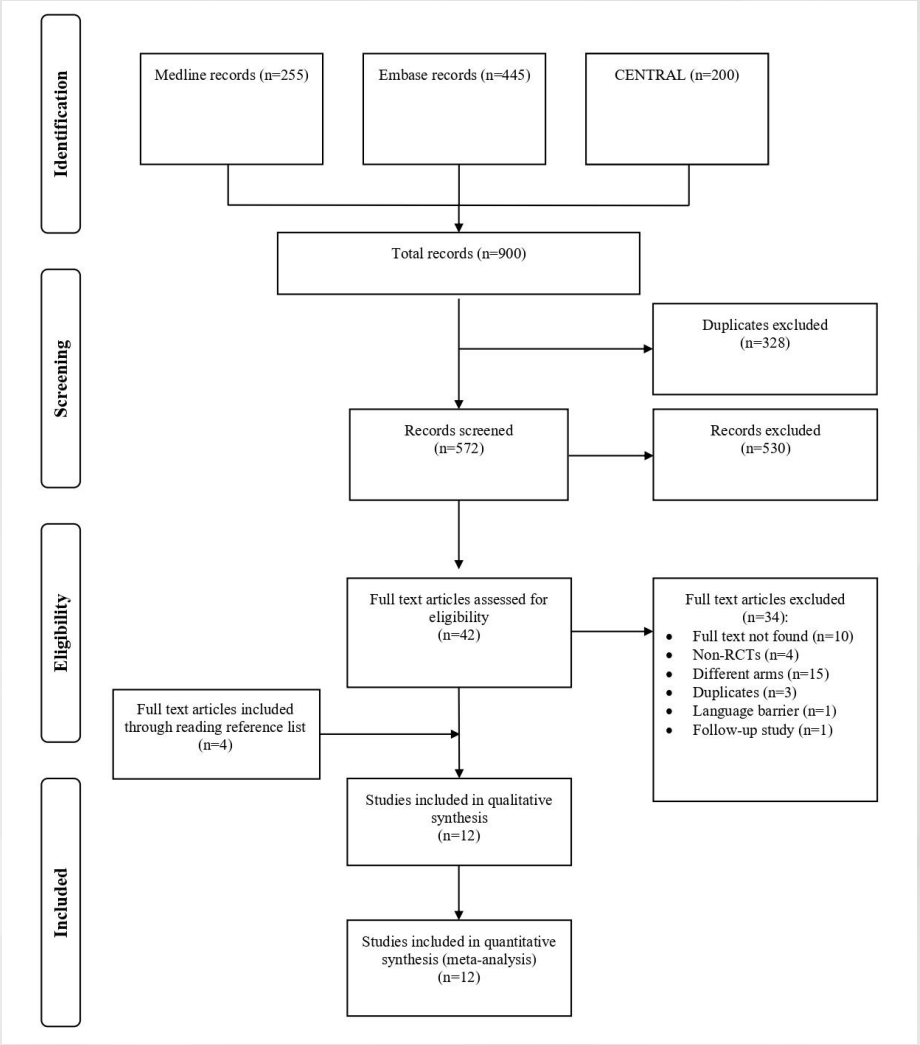

Figure 3: study flow diagram

CAG: conjunctival autograft
AMT: amniotic membrane transplantation
MMC: mitomycin C

Results: risk of bias and publication bias

- Low risk of bias: 5 studies.
- Some concerns: 5 studies.
- High risk of bias: 2 studies.
- **Publication bias:** funnel plots were symmetric.

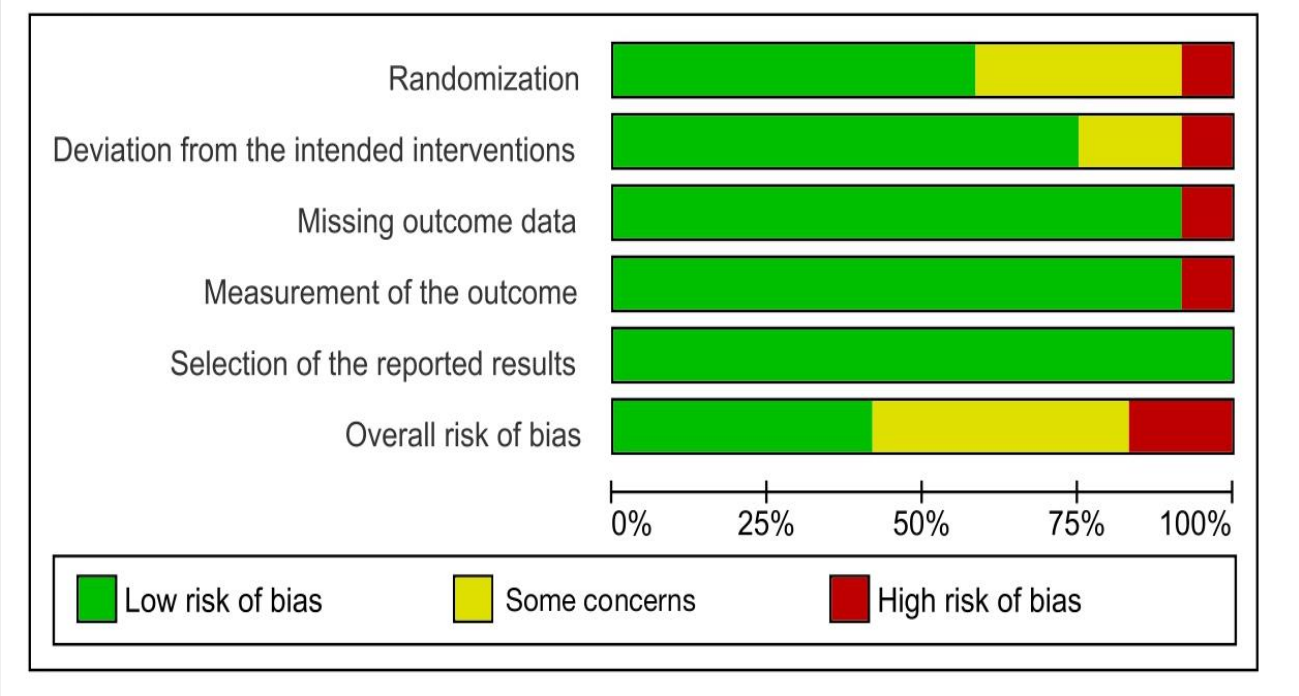

Figure: 4 risk of bias graph

Results: meta-analysis

Outcomes	Effect size	95% CI	P-value	I^2	GRADE
Outcomes reported as risk ratio					
CAG+MMC vs CAG alone					
Recurrence rate	0.12	0.02–0.63	**<0.05**	**0%**	**High**
Adverse events	1.81	0.40–8.31	0.44	28%	Low
AMT vs CAG alone					
Recurrence rate	1.51	0.63–3.65	0.36	73%	Low
Adverse events	0.46	0.22–0.95	**<0.05**	49%	Low

Table 2: summary of the results of the meta-analysis

CAG: conjunctival autograft
AMT: amniotic membrane transplantation
MMC: mitomycin C

Results: meta-analysis

- Recurrence rate

Study or Subgroup	CAG with MMC/AMT Events	Total	CAG without MMC Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
1.1.1 CAG with MMC							
Landau 2006	0	30	4	30	5.7%	0.11 [0.01, 1.98]	2006
Agahan 2014	0	17	0	15		Not estimable	2014
Martins 2019	1	20	11	29	8.4%	0.13 [0.02, 0.94]	2019
Subtotal (95% CI)		**67**		**74**	**14.0%**	**0.12 [0.02, 0.63]**	
Total events	1		15				
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%							
Test for overall effect: Z = 2.51 (P = 0.01)							
1.1.2 AMT							
Ma 2000	3	80	3	56	9.9%	0.70 [0.15, 3.34]	2000
Tananuvat 2004	18	39	2	41	10.6%	9.46 [2.35, 38.12]	2004
Luanratanakor 2006	37	148	13	106	13.6%	2.04 [1.14, 3.64]	2006
Cem 2007	1	27	1	28	6.1%	1.04 [0.07, 15.76]	2007
Liang 2012	10	52	6	81	12.4%	2.60 [1.00, 6.71]	2012
Toker 2015	5	39	2	43	9.8%	2.76 [0.57, 13.40]	2015
Prajna 2016	8	31	0	31	5.8%	17.00 [1.02, 282.30]	2016
Pan 2018	4	79	13	62	11.9%	0.24 [0.08, 0.70]	2018
Balakrishna 2020	0	45	8	45	5.8%	0.06 [0.00, 0.99]	2020
Subtotal (95% CI)		**540**		**493**	**86.0%**	**1.51 [0.63, 3.65]**	
Total events	86		48				
Heterogeneity: Tau² = 1.13; Chi² = 29.48, df = 8 (P = 0.0003); I² = 73%							
Test for overall effect: Z = 0.92 (P = 0.36)							
Total (95% CI)		**607**		**567**	**100.0%**	**1.06 [0.44, 2.55]**	
Total events	87		63				
Heterogeneity: Tau² = 1.38; Chi² = 38.70, df = 10 (P < 0.0001); I² = 74%							
Test for overall effect: Z = 0.13 (P = 0.90)							
Test for subgroup differences: Chi² = 7.00, df = 1 (P = 0.008), I² = 85.7%							

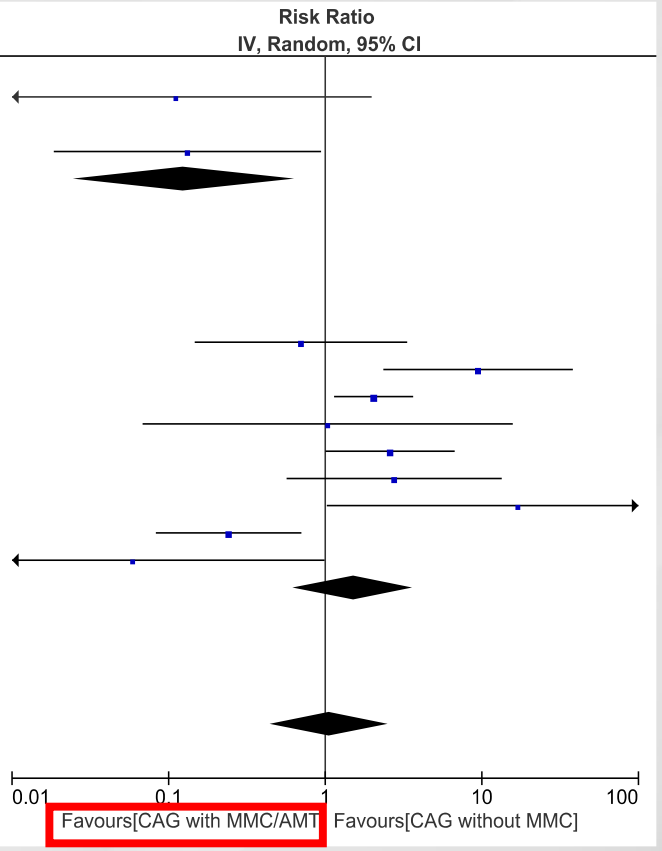

Figure 6: forest plot for recurrence rate

CAG: conjunctival autograft
AMT: amniotic membrane transplantation
MMC: mitomycin C

Results: meta-analysis

- Recurrence rate

CAG+MMC	CAG alone	AMT
1.4%	11.3%	16.5%

Table 3: recurrence rates following each approach.

CAG: conjunctival autograft
AMT: amniotic membrane transplantation
MMC: mitomycin C

Results: meta-analysis

- Adverse events

Study or Subgroup	CAG with MMC/AMT Events	Total	CAG without MMC Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
1.2.1 CAG with MMC							
Landau 2006	5	30	3	30	13.0%	1.67 [0.44, 6.36]	2006
Agahan 2014	0	17	1	15	4.2%	0.30 [0.01, 6.77]	2014
Martins 2019	6	36	0	29	4.9%	10.54 [0.62, 179.66]	2019
Subtotal (95% CI)		**83**		**74**	**22.0%**	**1.81 [0.40, 8.31]**	
Total events	11		4				
Heterogeneity: Tau² = 0.57; Chi² = 2.78, df = 2 (P = 0.25); I² = 28%							
Test for overall effect: Z = 0.76 (P = 0.44)							
1.2.2 AMT							
Ma 2000	2	80	6	56	11.1%	0.23 [0.05, 1.11]	2000
Tananuvat 2004	6	39	4	41	14.4%	1.58 [0.48, 5.17]	2004
Luanratanakor 2006	8	148	12	106	18.0%	0.48 [0.20, 1.13]	2006
Toker 2015	2	39	14	43	12.3%	0.16 [0.04, 0.65]	2015
Pan 2018	0	79	5	62	4.8%	0.07 [0.00, 1.27]	2018
Balakrishna 2020	7	45	9	45	17.5%	0.78 [0.32, 1.91]	2020
Subtotal (95% CI)		**430**		**353**	**78.0%**	**0.46 [0.22, 0.95]**	
Total events	25		50				
Heterogeneity: Tau² = 0.37; Chi² = 9.73, df = 5 (P = 0.08); I² = 49%							
Test for overall effect: Z = 2.10 (P = 0.04)							
Total (95% CI)		**513**		**427**	**100.0%**	**0.61 [0.30, 1.23]**	
Total events	36		54				
Heterogeneity: Tau² = 0.52; Chi² = 16.37, df = 8 (P = 0.04); I² = 51%							
Test for overall effect: Z = 1.38 (P = 0.17)							
Test for subgroup differences: Chi² = 2.52, df = 1 (P = 0.11), I² = 60.4%							

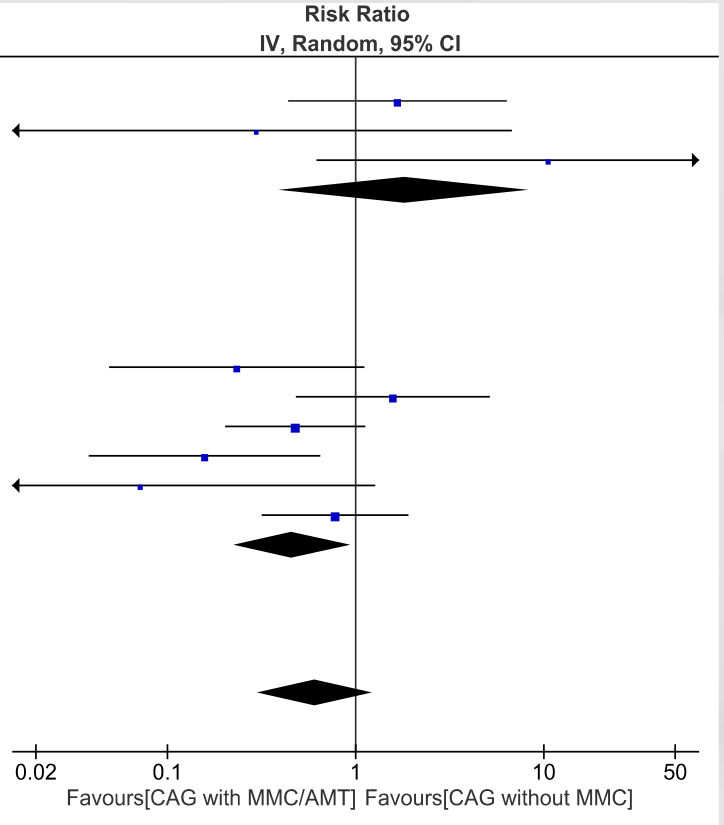

Figure 6: forest plot for adverse events

CAG: conjunctival autograft
AMT: amniotic membrane transplantation
MMC: mitomycin C

Discussion

❑Summary of the evidence:

- Our results on the superiority of CAG+MMC in terms of decreased rates of recurrence are consistent with those of a network meta-analysis of 2483 patients.[9]
- Our results that showed acceptable safety of CAG+MMC were in line with multiple long term observational studies that showed the use of intraoperative 0.02% MMC to be safe.[5,6]

❑ Strengths:

- RCTs.
- Original meta-analysis.

❑ Limitations:

- Variable follow up periods.

CAG: conjunctival autograft
AMT: amniotic membrane transplantation
MMC: mitomycin C

Conclusion

❑Implications on practice:

- A single intraoperative topical application of 0.02% MMC during excision of pterygium followed by CAG significantly has shown to decrease the rate of pterygium recurrence to 1.4% with no severe complications.
- A conventional route of administration, careful dosing, and patient selection are advisable.

❑ Implications on research:

- Future RCTs should implement a rigorous pre-study methodology and a sufficient follow-up period.

CAG: conjunctival autograft
AMT: amniotic membrane transplantation
MMC: mitomycin C

References

Thank You!