

# Surgical interventions for the primary prophylaxis of retinal detachment in Stickler Syndrome: a systematic review

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### INTRODUCTION

Stickler syndrome affects approximately 1 in 10,000 individuals. It is characterized by joint pain, facial abnormalities (eg. cleft lip and palate) and ocular abnormalities (eg. myopia). (Stickler 2001, 1965; Snead 1999). As many as 60% of individuals with Stickler syndrome experience retinal detachment (RD) and, consequently, are at a high risk of blindness. While RD can occur at any age, and the risk is life-long, the first RD in individuals with Stickler syndrome has been reported to occur most commonly in adolescence or early adulthood, between the ages of 10 and 30 years.

### METHODS

A systematic review to assess the effectiveness of surgical interventions to prevent RD in children and adults with Stickler syndrome. A systematic search was made in October 2009 of 12 databases of published and unpublished literature: MEDLINE; MEDLINE in process; EMBASE; CINAHL; The Cochrane Library; Biological Abstracts; Science Citation Index; UK Clinical Trials Research Network (UKCRN); National Research Register archive (NRR); Current Controlled Trials; Clinical Trials.gov; Annual Meeting of the Association for Research in Vision and Ophthalmology. There was no restriction by language, date or study design (other than the requirement that studies have a comparator group). Two reviewers double-screened all titles and abstracts of citations retrieved by the search to identify studies that satisfied the following inclusion criteria.

Population	Adults and children diagnosed with Stickler Syndrome (type 1 or 2)
Intervention and Outcome	Primary prophylactic surgery to prevent retinal detachment (RD) in eyes without any previous retinal detachment
Comparator:	Any
Study design	Comparative studies

Any disagreements were resolved by discussion or reference to the full paper. Both reviewers independently extracted and quality assessed all included studies. Narrative synthesis was performed.

### RESULTS

The literature search identified 1444 unique citations, of which 2 studies satisfied the inclusion criteria (Ang 2008; Leiba 1996). Both were retrospective cohort studies with control groups in populations diagnosed as having type 1 Stickler syndrome. Ang 2008 evaluated the prophylactic efficacy of 360° cryotherapy (204 participants) and Leiba 1996 focal or 360° circumferential laser treatment (22 participants). Participants in the control groups of both studies received either no prophylaxis or, in the case of an unknown number in the Ang 2008 study, prophylactic interventions other than cryotherapy (See Table 1).

**Table 1: Study characteristics and results**

Study	Study design	Population Age & gender	Intervention (N=patients)	Control (N=patients)	Follow-up	RD post-bilateral and unilateral prophylaxis n/N (eyes)	RD post- bilateral prophylaxis	RD post- unilateral prophylaxis
Ang <i>et al</i> 2008	Retrospective cohort study with controls	Type 1 Stickler Syndrome patients with GRTs and retinal detachment in one eye or no eye (N=204) Age range 2-92 years Gender: 109 male; 95 female	Bilateral and unilateral surgical prophylaxis "Standard prophylaxis": 360° cryotherapy Group 1: bilateral, i.e. both eyes (N=62) Group 2: unilateral, fellow eye only (N=31)	No prophylaxis or "non-standard prophylaxis", which included "treating isolated areas of lattice more posteriorly or using laser retinopexy" (N=111)	Group 1: range 1-27 years; (mean) 11.5 years Group 2: range 1-33 years; (mean) 15.5 years Control: "data on the timing of events were either unreliable or missing"	7/155 vs 134/222 RR: 0.07 (95% CI 0.04, 0.16), p<0.0001	4/124 vs 134/222 RR: 0.05 (95% CI 0.02, 0.14), p<0.0001	3/31 vs 134/222 RR: 0.16 (95% CI 0.05, 0.47), p=0.0009
Leiba <i>et al</i> 1996	Not reported; appears to be retrospective cohort study with controls	A family group of Type 1 Stickler Syndrome patients with ocular abnormalities (N=22) Age range: NR Gender: 11 male; 11 female	Bilateral and unilateral surgical prophylaxis (N=6) Circumferential laser treatment for eyes with extensive contiguous retinal lesions Focal laser treatment for eyes with small localised lesions of LD or isolated breaks	No prophylaxis (N=NR; reviewers calculate N=16)	Range: 1-15 years	1/10 vs 15/34 RR: 0.23 (0.03, 1.51), p=0.13	1/8 vs 15/34 RR: 0.28 (0.04, 1.84), p=0.19	0/2 vs 15/34 RR: 0.13 (0.01, 1.90), p=0.45

NR: Not reported; GRT: Giant Retinal Tear; LD: Lattice degeneration; CI: confidence interval. Note: These RRs have been calculated by the reviewers

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Both studies performed prophylaxis in individuals either with no previous RD in either eye, or performed prophylaxis in the fellow eye of those with a previous RD in the primary eye. Each study reported a statistically significant difference in the rate of RD per eye between the groups receiving prophylaxis and the controls. Relative risks (RR) were calculated by the review authors based on event data reported (See Table 1). There was a statistically significant reduction in the risk of RD for those exposed to cryotherapy for bilateral prophylaxis compared to the controls (RR: 0.05, 95% CI 0.02, 0.14, p<0.0001), as well as for unilateral prophylaxis (RR: 0.16, 95% CI 0.05, 0.47, p=0.0009). There was also a reduction in the risk of RD for those exposed to laser treatment for bilateral prophylaxis compared to the controls (RR: 0.28, 95% CI 0.04, 1.84, p=0.19), as well as for those exposed to unilateral prophylaxis (RR: 0.13, 95% CI 0.01, 1.90, p=0.45), but the relative reduction in risk was not statistically significant in either case. Neither study reported any major or long-term adverse events or complications associated with the interventions.

However, both studies are affected by a high risk of bias. The study design (retrospective cohort study with controls) is inherently weaker than prospective and randomized, controlled studies. It is also unclear in both studies whether possible participants had been excluded. The control group in Ang 2008 (cryotherapy) was substantially different from the intervention groups. A principal difference concerned the major confounding factor of age: the controls were much older (a mean age of 49 years compared to 21 and 36 years in the intervention groups). Given that the risk of RD is lifelong for this population, the control group was therefore inherently at greater risk of having experienced the primary outcome than the intervention groups. The duration of follow-up for the controls was also not reported, introducing further bias into the comparison between groups. The control group was also not homogenous as participants were exposed either to no prophylaxis or to a single type of prophylaxis. In Leiba 1996 (laser treatment) the sample was small (n=22), from a single family and no information was reported on the respective ages of the intervention and control groups. The degree of bias present was therefore even more difficult to determine. No mean duration of follow-up was reported for the intervention group, but the maximum follow-up was also much less than in the larger study (15 years versus 33 years). The relative estimate of effect generated by the data from these trials would almost certainly be reduced in any future, higher quality trial.

### CONCLUSIONS

The reduction in the risk of retinal detachment, based on the published data associated with the evaluated treatments, is large. However, both included studies have a high risk of bias. Future trials appropriate for rare conditions, such as non-randomized sequential allocation trials, are needed to reduce the lack of certainty surrounding the reported estimates of effect.