

The clinical effectiveness and safety of prophylactic retinal interventions to reduce the risk of retinal detachment and subsequent vision loss in adults and children with Stickler syndrome: a systematic review

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Executive summary

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Executive summary

Background

Stickler syndrome, also known as hereditary progressive arthro-ophthalmopathy, is an inherited progressive disorder of the collagen connective tissues. It is indicated by a variety of symptoms, and can affect the formation of the eyes, ears, palate, jaw and joints. Manifestations include short-sightedness, cataracts, retinal problems leading to retinal detachment (RD) and possible blindness, hearing loss, facial abnormalities including cleft palate and joint problems. Diagnosis can be confirmed by genetic analysis. Stickler syndrome is genetically heterogeneous with at least five subgroups, some with a high risk of ocular complications, others with no ocular involvement at all. The majority of patients have type 1 Stickler syndrome (MIM 108300), which is caused by mutation in the single gene that encodes type II collagen and has ocular, auditory, oro-facial and skeletal manifestations. This gene is called *COL2A1*. Types 2 and 3 Stickler syndrome are caused by mutations in the genes encoding type XI collagen. Unlike type II collagen, there are three genes encoding type XI collagen and they are *COL11A1*, *COL11A2* and *COL2A1*. Type 2 Stickler syndrome (MIM 604841) is due to mutations in the *COL11A1* gene and has ocular, auditory, oro-facial and skeletal manifestations. The *COL11A2* gene (mutations of which are responsible for type 3 Stickler syndrome – MIM 104840) is not expressed in the eye, and therefore this group of patients do not suffer eye problems and are more properly referred to as sufferers of otospondylomegaepiphyseal dysplasia. These patients have no ocular involvement, so they are not considered by this review.

Stickler syndrome is the most commonly identified inherited cause of RD in childhood. RD is a separation of the sensory retina from the retinal pigment epithelium, with an accumulation of vitreous fluid in the potential space between them. The rate of RD, potentially leading to loss of vision, in patients with Stickler syndrome has been suggested to be as high as about 60% in one eye. Whereas RD can take place at any age, and the risk is life-long, the first RD has been reported to occur most commonly in adolescence or early adulthood, between the ages of 10 and 30 years. There is therefore a potential case for early prophylactic intervention in those subgroups of patients with Stickler syndrome at the highest risk. Stickler syndrome is a comparatively rare condition and there are few reported data on prevalence, but the most commonly reported figure is one case in 10,000 people based on data from the USA. This figure is of limited reliability, however, given difficulties in diagnosis. Potential interventions, all of which seek to secure the retina and prevent RD, include cryotherapy, laser therapy and scleral buckling. Current service provision in the UK consists of no treatment, with or without monitoring; prophylaxis using 360° cryotherapy; or prophylaxis using laser treatment. There is no consensus regarding best practice and no current guidelines on prophylactic interventions for this population either in the UK or elsewhere.

Objectives

Firstly, to evaluate the clinical effectiveness of prophylactic retinal interventions for the primary prevention of RD in children and adults with Stickler syndrome. Secondly, to evaluate the safety (establish the numbers and types of adverse events or complications) associated with these interventions. Finally, to identify key areas for future primary research.

Methods

A systematic review was performed of the evidence for the clinical effectiveness and safety of primary prophylactic interventions for the prevention of RD in previously untreated eyes without RD in patients with Stickler syndrome. The primary outcome of interest was RD post prophylaxis. A systematic search was made of 11 databases for published and unpublished literature by an information specialist. These databases included MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing and Allied Health Literature and The Cochrane Library. 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 the citations retrieved by the search to identify studies that satisfied the inclusion criteria. Any disagreements were resolved by discussion or reference to the full paper. Both reviewers also independently extracted and quality assessed all included studies. The references of all included studies were also checked for further relevant citations. The authors of any studies with potential but unspecified Stickler syndrome patients within their study sample were also contacted to retrieve any additional, potentially relevant data on the efficacy of interventions in this population.

Results

The literature search identified 1444 unique citations, of which two studies satisfied the inclusion criteria. These studies were conducted in populations diagnosed with type 1 Stickler syndrome (and confirmed 'where possible' by genetic analysis) and constitute the principal evidence. Two further studies (three papers) conducted in patients with 'Wagner–Stickler' syndrome, an anachronistic term to describe a condition in which patients may have symptoms consistent with a diagnosis of Stickler syndrome (but unconfirmed by genetic analysis), were identified as possible supporting evidence. All of the included studies were identified from the search of the electronic databases.

The two Stickler syndrome studies were both retrospective cohort studies with control groups in populations diagnosed as having type 1 Stickler syndrome. One study evaluated the prophylactic efficacy of 360° cryotherapy on the post-oral retina (204 participants), and the other evaluated 360° circumferential laser treatment for eyes with extensive contiguous retinal lesions, where lesions were present in at least three quadrants of the retina, and focal laser treatment for eyes with small localised lesions of lattice degeneration or isolated breaks (22 participants). Participants in the control groups of both studies received either no prophylaxis or, in the case of an unknown number in the cryotherapy study, prophylactic interventions other than cryotherapy. Both studies either performed prophylaxis in individuals 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 also reported a statistically significant difference in the rate of RD per eye between the groups receiving prophylaxis (bilateral and unilateral combined) and the controls ($p < 0.0025$). 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 randomised controlled studies. It is also unclear in both studies whether possible participants had been excluded. The control group in the study of 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 with 21 and 36 years in the intervention groups). Given that the risk of RD is life-long 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 risk of bias into the comparison between the groups. The control group was also not homogeneous as participants were exposed either to no prophylaxis or to a single type of prophylaxis. In the study of laser treatment, the sample was small ($n = 22$) and from a single family, and no information was reported on the ages of the intervention and control groups. 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 vs 33 years).

The two small studies of patients reported to have been diagnosed with Wagner–Stickler syndrome reported inconsistent results. These studies are not included as principal trials, but as supporting evidence only, because of the quality and relatively small amount of relevant published evidence. One study compared laser treatment with scleral buckling and a range of other interventions (including cryotherapy) as prophylaxis in the fellow eye of patients who had had an RD in the primary eye (22 participants). The smallest number of RDs was reported for the scleral buckling intervention. The second study compared focal laser treatment or cryotherapy with two scleral buckling interventions, and reported no RDs in either group at follow-up of a maximum of 8 years. Both studies were affected by a high risk of bias: diagnostic criteria were unreported in one case; the follow-ups were short; comparability between groups was not assessed, nor was an assessment possible with the reported data; the sample sizes were small, and the results in the second study were unexpected and are potentially unreliable (no incidence of the primary outcome in any eye within the follow-up period).

Discussion

This is the first systematic review of prophylactic interventions for RD in Stickler syndrome. The review performed a highly sensitive search of the published and unpublished literature to identify potentially relevant studies. The principal author also contacted corresponding authors of studies who may have had a relevant but unspecified subgroup of Stickler syndrome patients within their study sample exposed to interventions for the primary prophylaxis of RD. No restrictions of language or date (non-English language articles were included) were applied, and the screening, data extraction and quality assessment were all performed independently by two reviewers. This approach reduced the potential for publication, selection and extraction bias.

The review found only four studies that satisfied the inclusion criteria, and all studies were retrospective cohort studies with comparator groups, which are more vulnerable to bias than some other study designs. The two principal studies of individuals diagnosed with type 1 Stickler syndrome both found a reduced risk of RD for those exposed to prophylaxis. However, the data reported in these studies do not permit the generation of a reliable estimate of effect for either cryotherapy or laser therapy compared with no prophylaxis: the efficacy of these interventions is therefore uncertain. This is because both studies are subject to a high risk of bias, either as a result of the lack of comparability between the intervention and control groups, especially in terms of the confounding factors of age and length of follow-up, or because the study evaluated only a small sample from a single family pedigree. In the absence of any good-quality studies directly comparing the two interventions, the relative efficacy of the two interventions is also uncertain. Neither study reported any major or long-term complications associated with the interventions, but the actual incidence and duration of minor complications is unknown. Despite the risk of bias in both studies and the uncertainty surrounding the relative effect of cryotherapy

and laser therapy in the primary prophylaxis of RD in type 1 Stickler syndrome, the rate of RD in the intervention groups of both studies was lower than the rate either experienced in the study control groups or reported in other studies of untreated Stickler syndrome populations not exposed to prophylaxis. These included subgroups of Stickler syndrome individuals under the age of 20 or 30 years, potentially the most comparable data. The ongoing reporting of follow-up data for the intervention groups in the largest principal study should potentially address some of the comparability issues between the intervention and control groups, principally differences in the confounding factor of age, but other issues affecting the comparability of the control group remain.

Conclusions

Only 360° cryotherapy and focal or 360° circumferential laser treatment have been evaluated for the type 1 Stickler syndrome population, and only then by a single retrospective, controlled, cohort study in each case. Both of these studies reported a significant difference between intervention and control groups (principally no treatment) and no major or long-term side effects or complications. However, there is a high risk of bias within these two studies, so the relative effectiveness of either 360° cryotherapy or focal and circumferential laser treatment in comparison with no treatment is uncertain. There is also no head-to-head trial comparing the two interventions, so their relative effectiveness in comparison with each other is also uncertain. A more reliable estimate of the relative efficacy of these interventions compared with no prophylaxis in terms of the prevention of RD and the frequency of complications could be generated by a high-quality randomised controlled trial comparing cryotherapy and laser treatment with each other and no treatment. The trial would require good baseline comparability between the intervention and control groups of type 1 Stickler syndrome individuals in terms of age and presence of RD in the primary eye, and adequate allocation concealment, and have a minimum follow-up of 10 years to offer data for interim analysis, but could be ongoing, given the life-long risk of the primary outcome. However, given the rarity of the condition, such a trial might be impractical. A non-randomised, prospective cohort comparison study, in which eligible participants are treated, followed up and analysed in one of these three study arms, is more realistic and practical. Such a study would potentially offer greater certainty in terms of the relative efficacy of both prophylaxis versus no prophylaxis and cryotherapy versus laser therapy than is possible with the currently available data. A service priority is also to determine reliably the prevalence of Stickler syndrome, i.e. how many individuals have type 1 or type 2 Stickler syndrome, and the risk of RD and subsequent blindness. Genetic analysis is required to establish the presence and type of Stickler syndrome. In summary, continued follow-up and analysis of study data, and data collection from relevant sample populations, are required to assess the long-term risks of blindness, RD and prophylaxis.

Publication

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NIHR Health Technology Assessment programme

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