Radioiodine therapy (RAI) for Graves’ disease (GD) and the effect on ophthalmopathy: a systematic review


CRD summary
The authors concluded that radioiodine therapy for Graves’ disease increased the risk of ophthalmopathy compared with antithyroid drugs. Prednisolone prophylaxis was beneficial for patients with pre-existing ophthalmopathy. This review was generally well conducted. However, a degree of caution might be required in interpreting these conclusions, given the limited amount of data available for each comparison in the review.

Authors’ objectives
To assess whether radioiodine therapy for Graves’ disease increased the risk of ophthalmopathy, and to determine the efficacy of glucocorticoid prophylaxis in the prevention of ophthalmopathy.

Searching
The following databases were searched without restriction on language and publication status from inception to August 2006: MEDLINE, EMBASE, BIOSIS Previews, CINAHL, HEALTHSTAR, and the Cochrane Central Register of Controlled Trials. Trial registries were also searched. Search terms were not reported. Study authors were contacted for relevant information.

Study selection
Randomised controlled trials (RCTs) and quasi-RCTs with a minimum follow-up of one year, in patients of any age with Graves’ disease defined using recognised criteria were eligible for inclusion. Only studies which compared radiotherapy with antithyroid drugs, surgery, radioiodine therapy with adjunctive anti-thyroid drugs, or radioiodine therapy with prophylactic glucocorticoids, were eligible for inclusion. The primary review outcomes were the occurrence or progression of ophthalmopathy, and the incidence of severe ophthalmopathy. Additional outcomes were hypothyroidism and adverse events.

More than half of the included RCTs evaluated eye outcomes after radioiodine therapy. Half of the included RCTs used prednisolone or betamethasone as glucocorticoid prophylaxis. All trials excluded patients with severe ophthalmopathy.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The quality of trials was assessed using the following criteria: allocation concealment, intention-to-treat analysis, comparability of groups at baseline, and blinding of outcome assessors.

Two reviewers independently performed the validity assessment, with any disagreements resolved by discussion.

Data extraction
It appears that the authors extracted data on the outcomes of interest and estimated relative risks (RRs) with 95% confidence intervals.

Two reviewers independently extracted the data from studies, with any disagreement resolved by discussion.

Methods of synthesis
The studies were combined in meta-analyses using a random-effects model. Pooled relative risks, with 95% confidence intervals, were calculated. Statistical heterogeneity was assessed using the $I^2$ statistic.
Results of the review

Ten randomised controlled trials (RCTs) were included in meta-analyses (n=1,226 patients). The sample size ranged from 40 to 450. None of the patients permanently lost vision. Methodological quality varied between trials. Concealment allocation was inadequate in most trials. The follow-up duration of RCTs ranged from one to 4.6 years.

When the trials were pooled, radioiodine therapy was associated with a significantly increased risk of developing or worsening ophthalmopathy compared with antithyroid drugs (relative risk 4.23, 95% confidence interval (CI): 2.04 to 8.77; two RCTs), and an increased risk of severe ophthalmopathy (relative risk 4.35, 95% CI: 1.28 to 14.73; two RCTs). There was no statistically significant increased risk when radioiodine was compared with thyroidectomy and radioiodine with adjunctive antithyroid drugs.

Prednisolone prophylaxis was associated with a significant effect on the prevention of worsening of eye disease in patients with pre-existing ophthalmopathy (relative risk 0.03, 95% CI: 0.00 to 0.24; two RCTs), but not in patients without pre-existing ophthalmopathy. There was no significant effect of betamethasone on the prevention of ophthalmopathy.

Statistically significant heterogeneity was only observed in the outcome of ophthalmopathy for the comparison between radioiodine with prophylactic steroids and radioiodine therapy alone (I² =62.2%, p=0.02).

Authors' conclusions

Radioiodine therapy for Graves' disease increased the risk of ophthalmopathy when compared with antithyroid drugs, but not when compared with thyroidectomy or with radioiodine plus adjunctive antithyroid drugs. Prednisolone prophylaxis was beneficial for patients with pre-existing ophthalmopathy.

CRD commentary

This review's inclusion criteria were clear. Several relevant databases were searched. Efforts were made to find both published and unpublished studies without language restriction, minimising the potential for both publication and language biases. Steps were taken to minimise bias by having more than one reviewer undertake the validity assessment and data extraction, but it was unclear whether the process of study selection was also performed in duplicate. Relevant criteria were used to examine the study quality.

Statistical heterogeneity was assessed and appropriate statistical methods were used to pool the results. Although significant heterogeneity was found in the outcome of ophthalmopathy for the comparison between radioiodine with prophylactic steroids and radioiodine therapy alone, the trials generally showed the same direction of effects. This review was generally well conducted in most respects and the authors' conclusions reflected the evidence presented. However, a degree of caution might be required in interpreting these conclusions, given the limited amount of data available for each comparison in the review.

Implications of the review for practice and research

Practice: The authors stated that a minimum specialist follow-up of 12 months following radioiodine therapy is required, and that prednisolone prophylaxis should be standard practice in preventing the progression of ophthalmopathy for patients with mild pre-existing ophthalmopathy.

Research: The authors did not state any implications for research.

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Bibliographic details

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.