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Lieder A, Khan MK, Lippert BM

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Photodynamic therapy for recurrent respiratory papillomatosis.
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[Intervention Review]

Photodynamic therapy for recurrent respiratory papillomatosis

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ABSTRACT

Background

Recurrent respiratory papillomatosis (RRP) is a benign condition of the mucosa of the upper aerodigestive tract. It is characterised by recurrent papillomatous lesions and is associated with human papillomavirus (HPV). Frequent recurrence and rapid papilloma growth are common and in part responsible for the onset of potentially life-threatening symptoms. Most patients afflicted by the condition will require repeated surgical treatments to maintain their airway, and these may result in scarring and voice problems. Photodynamic therapy introduces a light-sensitising agent, which is administered either orally or by injection. This substance (called a photo-sensitiser) is selectively retained in hyperplastic and neoplastic tissue, including papilloma. It is then activated by light of a specific wavelength and may be used as a sole or adjuvant treatment for RRP.

Objectives

To assess the effects of photodynamic therapy in the management of recurrent respiratory papillomatosis (RRP) in children and adults.

Search methods

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; Cambridge Scientific Abstracts; ICTRP and additional sources for published and unpublished trials. The date of the search was 27 January 2014.

Selection criteria

Randomised controlled trials utilising photodynamic therapy as sole or adjuvant therapy in participants of any age with proven RRP versus control intervention. Primary outcome measures were symptom improvement (respiratory distress/dyspnoea and voice quality), quality of life improvement and recurrence-free interval. Secondary outcomes included reduction in the frequency of surgical intervention, reduction in disease volume and adverse effects of treatment.

Data collection and analysis

We used the standard methodological procedures expected by The Cochrane Collaboration. Meta-analysis was not possible and results are presented descriptively.

Main results

We included one trial with a total of 23 participants. This study was at high risk of bias. None of our primary outcomes and only one of our secondary outcomes (reduction in volume of disease, assessed endoscopically) was measured in the study. There was no significant difference between the groups (very low-quality evidence). Adverse effects reported included airway swelling requiring intubation in a child with severe RRP a few hours after photodynamic therapy.

Authors' conclusions

There is insufficient evidence from high-quality randomised controlled trials to determine whether photodynamic therapy alters the course of disease or provides an added benefit to surgery in patients with recurrent respiratory papillomatosis. Multicentre randomised controlled trials with appropriate sample sizes and long-term follow-up are required to evaluate whether photodynamic therapy is of benefit. Outcomes such as improvement in symptoms (respiratory function and voice quality) and quality of life should be measured in future trials.

PLAIN LANGUAGE SUMMARY

Photodynamic therapy for recurrent respiratory papillomatosis

Background

Recurrent respiratory papillomatosis is a condition of the mucosal lining of the upper airway, which leads to multiple benign, wart-like growths (papilloma). Although not cancerous, it can lead to serious problems, including hoarseness and airway obstruction. The main treatment is repeated surgical removal of the papilloma using a laser or cutting instrument. However, multiple surgical procedures carry the risk of complications and can also result in long-term scarring. Photodynamic therapy works through the application of a light-sensitising substance, which is then activated by light of a specific wavelength. A chemical reaction creates powerful active molecules that destroy the papilloma locally. It can be used on its own or as an additional treatment together with surgical removal. It has been proposed that photodynamic therapy slows the growth of the papilloma and results in fewer recurrences and therefore fewer surgical procedures.

Study characteristics

We found one randomised controlled trial with a total of 23 participants for inclusion in this review. The study took place at two centres in the USA. Six of the 23 patients did not complete the study (dropped out). Participants who completed the study were outpatients, their age range was four to 60 years and 76% were men and 24% women. The study did not measure any of the outcomes important to patients (symptom improvement - respiratory distress/dyspnoea and voice quality, quality of life improvement and recurrence-free interval). It did measure the reduction in the volume of disease (assessed with an endoscope).

Key results

We found insufficient evidence from the included study that photodynamic therapy has a benefit on its own or in combination with surgery in recurrent respiratory papillomatosis. There was no clear evidence that effects observed in the treatment group were different to those in the control group. Adverse effects reported included airway swelling in a child with severe disease a few hours after photodynamic therapy, which required insertion of a breathing tube and a prolonged stay in hospital.

Quality of the evidence

The overall quality of the evidence is very low: there was no blinding of treatment and a high rate of drop-out. This evidence is up to date to January 2014.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Photodynamic therapy for recurrent respiratory papillomatosis

Patient or population: 23 patients aged two years or older with recurrent respiratory papillomatosis

Settings: day-case surgery

Intervention: photodynamic therapy plus co-intervention (surgical debridement)

Comparison: control intervention (surgical debridement)

Outcomes	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Primary outcome: improvement in symptoms (respiratory distress/dyspnoea)	—	—	Not measured
Primary outcome: improvement in symptoms (voice quality)	—	—	Not measured
Primary outcome: improvement in quality of life	—	—	Not measured
Primary outcome: recurrence-free interval	—	—	Not measured
Reduction in mortality	—	—	Not measured
Reduction in number and/or frequency of surgical interventions and/or time until first relapse requiring surgery	—	—	Not measured
Reduction in number and/or duration of hospital stay(s)	—	—	Not measured
Reduction in volume of disease, assessed endoscopically	23 (1 study)	⊕⊖⊖⊖ **very low** [1]	No statistically significant difference between treatment and control groups Study is insufficiently powered

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Evidence judged to be of very low quality due to the risk of bias: downgraded due to lack of blinding and high drop-out rate, and because it is insufficiently powered.

BACKGROUND

Description of the condition

Recurrent respiratory papillomatosis (RRP) is a benign condition of the mucosa of the upper aerodigestive tract characterised by multiple recurrences. It mainly affects the larynx and trachea and can occur in both children and adults. Excessive epithelial proliferation leads to formation of multiple papillomata that add bulk to the mucosa, and may lead to symptoms of dysphonia, obstruction of the upper airway, stridor and respiratory distress. RRP can be life-threatening if left untreated. Frequent recurrence and rapid growth of papilloma is common and is in part responsible for the onset of potentially life-threatening symptoms. Before endoscopic surgery of papilloma was established as a treatment modality, a tracheotomy was considered the standard treatment for severe RRP for both paediatric and adult patients (Cole 1989).

RRP is associated with human papillomavirus (HPV), most commonly type 6 and 11, although type 16 and 18 (associated with malignancies in the genital and aerodigestive tract) and 31 and 33 have also been isolated from respiratory papillomata (Derkay 2008). A commensal virus in humans, HPV may exist as a latent infection of the upper aerodigestive tract mucosa. This is thought to be the source of the disease and explains its recurrence. Widespread infection would normally be suppressed by the host immune system, but it has been suggested that the immune response to HPV proteins in patients with RRP is altered, resulting in restriction of CD4 and CD8 lymphocyte activity, promotion of immune tolerance and dysfunction of natural killer cells, essentially preventing effective control of HPV type 6 and 11 infection (Bonagura 2010).

There is a degree of spontaneous resolution of papilloma, but the reason for this is as yet unknown. A large Canadian study of 243 cases of juvenile-onset RRP showed that 64% of cases had a decreasing number of surgeries per year when there was no adjuvant intervention (Campisi 2010). A smaller study in children revealed that the frequency of surgical procedures varies, even when no adjuvant treatment is given (Ongkasuwan 2012), but the cause for this variability is not yet understood. However, most patients afflicted by the condition will require repeated treatments to maintain their airway and these in themselves may lead to scarring and voice problems.

Malignant transformation into squamous cell carcinoma is a rare complication of RRP (Gallagher 2008; Lin 2010).

The mainstay of treatment, especially for aggressive papillomata, is surgical subtotal clearance of the papillomata in the upper airway using cold steel instrumentation, laser or, more recently, powered microdebrider. Due to the recurrent nature of papillomata, multiple surgical procedures are required over the course of a lifetime, the frequency of which may range from every few weeks to once a year (Derkay 2008). Surgical techniques have evolved over time and most surgeons will now use a powered microdebrider to remove the papillomata from the upper aerodigestive tract. When compared with laser, the powered microdebrider offers more precise removal of lesions (Imaizumi 2012); it also leads to less scarring, with a lower risk of adhesions or stenosis. There is therefore a lower cumulative risk of these complications and less morbidity from multiple surgical procedures (Pasquale 2003).

In addition to surgery, adjuvant treatment has been proposed to reduce the frequency and severity of recurrent papilloma growth. One of the earliest adjuvant treatments was the systemic application of interferon-alpha, which is thought to modulate the host immune response by inhibiting viral protein synthesis (Sen 1982). Targeting of viral replication and immunomodulation by intralesional injection of antiviral agents such as cidofovir has not been shown to be beneficial when used alone or as an adjuvant to surgery (Chadha 2010). Observation of severe side effects of cidofovir, such as progressive dysplasia and renal failure, has led to its manufacturer issuing a warning and a recommendation to limit its use to cytomegalovirus-induced infections in patients with AIDS (Kusnick 2011; Wemer 2005). Strategies to eradicate viral colonisation by administration of a vaccine may reduce the incidence of RRP in the future, but selection of vaccinated individuals (usually adolescent females), variation in the types of HPV included in the vaccine and inconsistent uptake mean that RRP will be far from eradicated in the near future (Kumar 2011).

Description of the intervention

Photodynamic therapy is a minimally invasive, low-toxicity treatment strategy. Its key components consist of a photosensitising agent, a light source and tissue oxygen. It utilises molecular energy exchange between visible light and a photosensitising agent, which results in the formation of highly reactive cytocidal oxygen species. Photodynamic therapy is thought to have originated in ancient Egypt or India, where plant essences and sunlight were used for treating vitiligo and other skin conditions. Modern photodynamic therapy was developed in chemical dye-producing laboratories in Germany, following the observation of a phototoxic effect in combination with light. The phrase 'photodynamic action' was coined by von Tappeiner in the early 20th century when he reported successful treatment of basal cell carcinoma of the facial skin using 1% eosin activated by sunlight or arc-lamp light (von Tappeiner 1903). Photodynamic therapy has been used and refined over the last century. One of the milestones in its development was the discovery of haematoporhyrin derivative (HpD), first described by Lipson and colleagues. It was subsequently successfully used on cutaneous malignant tumours by Dougherty and colleagues at the Roswell Park Cancer Institute in New York (Dougherty 1978; Lipson 1961).

Standard photosensitising agents belong to three chemical groups (chlorophylls, porphyrins and dyes), which can be applied topically or systemically (Lippert 2002). M-tetra(hydroxyphenyl) chlorin (m-THPC) or temoporfin is a second-generation photosensitiser molecule based on chlorine. It is applied systemically by intravenous injection. Aminolevulinic acid (ALA), a porphyrin, can be applied topically or by oral ingestion. Photosensitisers used in photodynamic therapy for RRP and malignant tumours of the head and neck have included HpD, dihaematoporphyrin ether (DHE), ALA and m-THPC.

If applied systemically, the major side effect of photosensitisers is generalised photosensitisation. This was more pronounced with early, first-generation photosensitising agents such as HpD and patients often had to spend days and weeks in darkened rooms. With modern generation agents, this is less marked, but patients are advised to avoid direct sunlight for a few weeks following treatment.

The absorption wavelength of a photosensitising agent is between 630 nm (HpD) and 652 nm (m-THPC). Light generated by laser is often used as an activator, but its cost and complexity have somewhat limited its widespread use in photodynamic therapy. New photodiode technology light sources that favour an interstitial light delivery system with prolonged photoactivation have not only made this intervention more accessible, but potentially also more efficient (Chen 2002; Lippert 2002). Photodynamic therapy technology is progressively being expanded to include new light-emitting diode (LED) technology. Whereas in conventional photodynamic therapy the photosensitised tissue was exposed to intense light for seconds to minutes, resulting in the production of powerful oxidants for a short period only, the novel, longer interstitial light delivery system leads to prolonged or repeated photoactivation of photosensitising agents, resulting in a larger number of cytocidal oxygen molecules in individual cells, increased cell death and increased volume and depth of photodynamic therapy-induced tissue necrosis (Armbruster 2002; Chen 2002). This may result in higher efficacy of photodynamic therapy, especially in bulky disease.

How the intervention might work

Photodynamic therapy works by selectively killing pathological cells and tissues through the local generation of highly toxic singlet oxygen and other toxic oxygen radicals following activation of the photosensitising agent by light. Cell death is achieved through necrosis or apoptosis and is highly localised, causing little collateral damage. Hypoxic or low turnover tissues are less affected. The effective agent binds to lipoproteins in the cell membrane and in cellular organelles such as endoplasmatic reticulum, mitochondria and lysosomes. Photodynamic damage to the endoplasmatic reticulum of the mitochondria leads to loss of function of anti-apoptosis proteins of the Bcl-2 family, which then leads to increased release of pro-apoptotic proteins, which bind to the mitochondrial membrane and create pores that lead to the release of mitochondrial cytochrome C into the cytosol. This initiates one of the signalling pathways for the initiation of apoptosis. Apoptosis is a non-inflammatory process of cell death that leads to activation of endonucleases, cleavage of DNA and activation of proteases, leading to breakdown of the cell into fragments that can be ingested by adjoining cells. Photosensitisers binding to the cell membrane alter membrane properties and also migrate into the cytosol where they cause inactivation of apoptotic proteins and promote cell death by necrosis. Necrosis results in damage to the cell membrane and release of lysosomal proteases, which results in an IL-6 (interleukin-6) mediated inflammatory response; this may have a partial role in immune-mediated destruction of the tumour tissue (Armbruster 2002; Chen 2002).

Photodynamic therapy appears to result in a time-delayed response. Non-controlled and non-randomised controlled trials suggest that photodynamic therapy appears to increase the recurrence-free interval and reduce the number of surgical procedures needed to maintain a safe airway between six and 12 months after treatment, with most patients being disease-free (Abramson 1994; Shikowitz 1998; Shikowitz 2005). This has been shown to be sustained for three to five years, with reduced numbers of procedures after five years (Feyh 1993; Shikowitz 2005).

Why it is important to do this review

The frequent recurrence and potentially life-threatening airway obstruction of this condition mean that many patients would chose surgical management of recurrences rather than wait for the effect of photodynamic therapy to become apparent. However, regular endoscopies with photodocumentation and removal of papillomata where there are airway concerns have already been incorporated into some trial protocols (Shikowitz 2005). An alternative option would be to offer photodynamic therapy as an adjuvant treatment modality at the time of endoscopy and papilloma removal (as described in the protocol Lippert 2002), combined with regular endoscopies and removal of papilloma when necessary.

Although a benign condition, RRP is a potentially devastating disease with significant morbidity. The mainstay of treatment is surgery, but there are no national or international guidelines on its management. Photodynamic therapy has been reported to improve the voice and airway and to slow the recurrence of papillomata. It may provide a valuable alternative therapeutic option (Derkay 2001). Currently there are no systematic reviews of available data. This review will evaluate the effectiveness of photodynamic therapy in the management of RRP.

OBJECTIVES

To assess the effects of photodynamic therapy in the management of recurrent respiratory papillomatosis (RRP) in children and adults.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Participants of any age with RRP.

Types of interventions

We differentiated whether photodynamic therapy was used on its own or as an adjuvant intervention, and included the following types and groupings of interventions:

- Photodynamic therapy versus no intervention
- Photodynamic therapy versus inactive control intervention
- Photodynamic therapy versus active control intervention
- Photodynamic therapy plus co-intervention versus no intervention
- Photodynamic therapy plus co-intervention versus inactive control intervention
- Photodynamic therapy plus co-intervention versus active control intervention
- Photodynamic therapy plus co-intervention versus co-intervention only (only difference is photodynamic therapy)
- Photodynamic therapy plus co-intervention versus co-intervention only plus inactive co-intervention (only difference is photodynamic therapy)

- Photodynamic therapy plus co-intervention versus co-intervention only plus active co-intervention (only difference is photodynamic therapy)

Types of outcome measures

We identified the following primary and secondary outcomes for this review. The primary aim of treatment is improvement of patient symptoms and patient quality of life as well as prolongation of recurrence-free interval. Secondary outcomes include objective findings such as reduction of mortality, reduction of the number of operative procedures and hospitalisation, as well as appearance as assessed by endoscopy.

Primary outcomes

1. Improvement in symptoms: respiratory distress/dyspnoea, measured by validated questionnaire or lung function testing.
2. Improvement in symptoms: voice quality, measured by voice quality score or inventory (validated subjective or objective measures were preferable. We planned to assess other measures on an individual basis to ensure they did not incorporate an unacceptable risk of bias).
3. Improvement in quality of life (validated quality of life measures were acceptable).
4. Recurrence-free interval.

Secondary outcomes

1. Reduction in mortality.
2. Reduction in number and/or frequency of surgical interventions and/or time until first relapse requiring surgery.
3. Reduction in number and/or duration of hospital stay(s).
4. Reduction in volume of disease, assessed endoscopically.
5. Adverse effects.

Search methods for identification of studies

We conducted systematic searches for randomised controlled trials. There were no language, publication year or publication status restrictions. The date of the search was 27 January 2014.

Electronic searches

We searched the following databases from their inception for published, unpublished and ongoing trials: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL 2013, Issue 12); PubMed; EMBASE; CINAHL; AMED; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; ISRCTN; ClinicalTrials.gov; ICTRP; Google Scholar and Google. In searches prior to 2013, we also searched BIOSIS Previews 1926 to 2012.

We modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, we combined subject strategies with adaptations of the highly sensitive search strategy designed by The Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b (Handbook 2011)). Search strategies for major databases including CENTRAL are provided in Appendix 1.

Searching other resources

We scanned the reference lists of identified publications for additional trials and contacted trial authors where necessary. In addition, we searched PubMed, TRIPdatabase, *The Cochrane Library* and Google to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials. We searched for conference abstracts using the Cochrane Ear, Nose and Throat Disorders Group Trials Register.

Data collection and analysis

Selection of studies

Two authors (A Lieder, M Khan) independently screened all titles and abstracts identified in the search utilising a flow chart designed for this systematic review and identified potentially relevant studies. We obtained full-text articles of all potentially relevant studies. We recorded the studies that we excluded from the review with reasons for exclusion in the Characteristics of excluded studies table. We resolved any differences in study selection by discussion or referral to a third author (B Lippert).

Data extraction and management

Two authors (A Lieder, M Khan) independently extracted data from the studies using a standardised data form. Following verification of study eligibility, we extracted the following data:

- Country of study
- Hospital
- Year the trial was conducted
- Type of trial design
- Number of treatment groups
- Data collection time points
- Participant characteristics, inclusion criteria and exclusion criteria
- Generation of allocation sequence, concealment of allocation sequence, blinding, etc.
- Intervention details (agent, dose, mode of delivery, timing and length of intervention, withdrawal/losses)
- Primary/secondary outcomes and adverse events

The first author (A Lieder) entered data from the included study into the Cochrane Review Manager 5 (RevMan) software (RevMan 2012); another author (M Khan) reviewed all data and confirmed that the correct data had been extracted and in the correct format. Where necessary and where data from the study were not provided, we wrote to the authors of the study requesting further information.

Assessment of risk of bias in included studies

Two authors (A Lieder, M Khan) independently assessed risk of bias in the included studies. Any disagreements were resolved by discussion or arbitrated by B Lippert.

We assessed the risk of bias in the included trials using the domains outlined in Chapter 8 of the*Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

- sequence generation (randomisation);
- allocation sequence concealment;
- blinding of study participants and investigators;

- blinding of outcome assessment
- incomplete outcome data and withdrawal of participants;
- selective outcome reporting; and
- other sources of bias.

We evaluated the quality of studies using The Cochrane Collaboration's 'Risk of bias' tool and we created a 'Risk of bias' table for the included study in RevMan 5 (RevMan 2012). This involved describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias.

Measures of treatment effect

We measured treatment effect according to data format. For dichotomous data, we planned to use risk ratio (RR) and for continuous data, mean difference (MD) or standard mean difference (SMD). If time-to-event data were reported, we would have explored whether these data could be analysed as dichotomous data by means of the risk ratio. For this version of the review quantitative data analysis was not possible as only one eligible study was identified. We will apply these methods in future updates if additional data are available.

Unit of analysis issues

We planned to assess whether the included studies presented results for more than one point in time. If this was the case, we would have defined several different outcomes based on different time points in follow-up and performed separate analyses for short-term and long-term follow-up where applicable. This was not required in the current version of the review.

Dealing with missing data

The first author (A Lieder) contacted the study authors to ask whether data not reported in the studies were available. Where data were not available, we planned to conduct the analysis with the available data only. We would have discussed the potential impact of missing data on the findings of the review. We would have performed a sensitivity analysis to assess how sensitive the results were to changes in the assumptions that were made. We received a response from the included study authors with the conclusion that further data were not available and we therefore conducted the analysis with the published data only.

Assessment of heterogeneity

We had planned to explore heterogeneity of the included studies using the Chi^2 test and I^2 statistic and by subgroup analysis where applicable. We would have endeavoured not to exclude studies once they had been included to prevent the introduction of bias. However, if the situation of heterogeneity due to some outlying studies had arisen, we had planned to perform the analysis with and without outlying studies.

Assessment of reporting biases

We performed a comprehensive search for published and unpublished studies using multiple online and other sources. Using our knowledge of ongoing studies and the experience of our co-author (Lippert BM), we identified unpublished studies and studies reported in languages other than English. We searched for suitable unpublished studies from trial registers. We made every effort to avoid multiple publication bias by contacting study authors where applicable.

Data synthesis

One author (A Lieder) performed data analysis using the data from one included study. As only one study was eligible, analysis pooled data was not possible. If additional data become available, we will use meta-analysis for homogenous data in future updates. If data are heterogenous, we will perform subgroup analyses where applicable.

Subgroup analysis and investigation of heterogeneity

Investigation of heterogeneity was not required with the present data. We planned to perform subgroup analysis where applicable. Potential subgroup analyses would be in subsets of participants: paediatric patients as defined by the study authors and adult patients as defined by the study authors. We also planned to perform a subgroup analysis based on ethnicity of included study participants where applicable.

Sensitivity analysis

We planned to perform sensitivity analysis in case of missing data and for risk of bias. If measurement of treatment effect was reported using a variable type of data (dichotomous, continuous or time-to-event), we also considered a sensitivity analysis. In addition, we planned to identify further potential factors requiring the undertaking sensitivity analysis during the review process. If these showed uncertainty, we would have contacted the study authors for further data to resolve uncertainty. In this version of the review, these methods could not be applied as only one study was included in the analysis.

Summary of findings

We created a 'Summary of findings' table according to the recommendations in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). The outcomes included were: improvement in symptoms (respiratory distress/dyspnoea); improvement in symptoms (voice quality); improvement in quality of life; recurrence-free interval; reduction in mortality; reduction in number and/or frequency of surgical interventions and/or time until first relapse requiring surgery; reduction in number and/or duration of hospital stay(s) and reduction in volume of disease, assessed endoscopically.

RESULTS

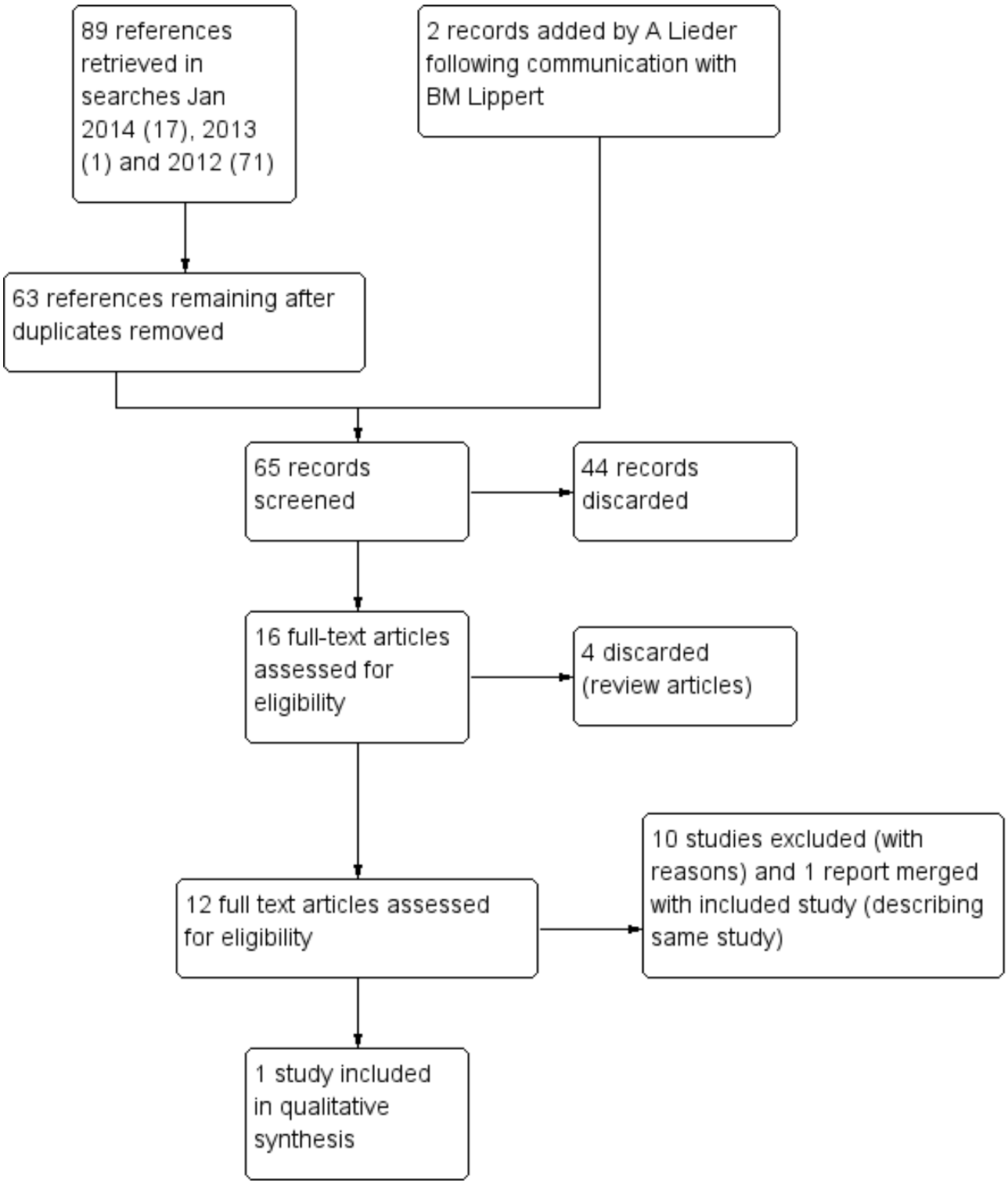
Description of studies

Results of the search

The search for eligible studies, conducted in January 2014, yielded 72 references (Figure 1). After duplicates were excluded, 54 references remained and we assessed the titles and abstracts for eligibility. Out of these, we considered 16 references to be potentially relevant and retrieved them in full. Of these, two were reports in Russian and two were in German. We considered 12 references to be reports of potentially eligible randomised controlled trials. The other four reports were review articles and we discarded them; however, on studying the full-text reports we identified one book chapter (Lippert 2002), and one additional report (Leunig 2000), which contained potentially eligible studies. Upon evaluation of these 12 full-text studies, one was found

to be a randomised controlled trial and was included in the analysis (Shikowitz 2005). We excluded 10 studies (Abrahamson 1992; Abramson 1994; Feyh 1993; Feyh 1995; Leunig 2000; Lippert 2002; Ronn 1996; Shikowitz 1998; Sokolov 2007; Sokolov 2010) (see Excluded studies). One report described an ongoing study, which was later completed and is the study included in this review (Shikowitz 2005). There are no ongoing studies or studies awaiting assessment at present.

Figure 1. Process of sifting search results and selecting studies for inclusion.



Included studies

See Characteristics of included studies table.

Design

The included study was a multicentre, randomised, controlled, parallel-arm study.

Sample size

The study enrolled 23 participants and 17 were included in the analysis.

Setting

The study took place in two centres in New York State, USA as day-case surgery.

Participants

Patients older than two years with clinically proven RRP requiring surgical removal three or more times per year were eligible for inclusion in the study. Of 17 patients who completed the study, 13 (76%) were male and four (24%) were female. The age range was from four to 60 years at the time of enrolment (no mean age given). Fifteen patients (88%) were of white ethnic origin, one patient (6%) was African American and one patient (6%) was of Hispanic origin.

Interventions

Five months after enrolment, patients were randomised into one of two treatment groups. The first group (early group) received PDT at six months after enrolment. The second group (late group) received PDT at 18 months after enrolment. The late group served as a control for the early group. Based on earlier findings by the same authors (Shikowitz 1998), patients received meso-tetra (hydroxyphenyl) chlorin (m-THPC) at a dose of 0.15 mg/kg body weight intravenously. Six days following the administration of m-THPC, all participants received photodynamic therapy during an upper airway endoscopy, using 652 nm diode laser activating light at 80 to 100 J for adults and 60 to 80 J for children (depending on the plasma concentration of m-THPC at the time of photodynamic therapy). The first treatment group, known as the early group, received photodynamic therapy six months after enrolment. The second treatment group, known as the late group, received photodynamic therapy 18 months after enrolment.

Outcomes

Shikowitz 2005 assessed some but not all of the outcomes defined in our protocol. None of our predefined primary outcome measures were assessed in the study. The reduction of disease volume as defined by a papilloma score (secondary outcome) was assessed at regular intervals by the study authors.

Patients underwent an upper airway endoscopy at enrolment and then every three months for the duration of the study. At each endoscopy, the extent of the papilloma was scored and photographically documented. Papillomata were removed if necessary to maintain a safe airway and the growth rate of papillomata was used as an outcome measure. The primary unit of analysis was the participant's average papilloma score per day. The change in percentage score between time of randomisation to initial surgery and after photodynamic therapy was analysed and given as a percentage.

Other parameters measured were plasma concentration of m-THPC, presence of HPV DNA in clinically normal biopsies following photodynamic therapy, and expression of interferon-gamma and interleukin-10 messenger RNA cytokines as a measure of host immune response.

The initial power analysis for this study determined that 28 patients would be required in each arm to demonstrate a 50% difference in growth rate. However, enrolment into the study was limited by patient concern about one of the treatment groups having to wait 18 months before commencement of photodynamic therapy, and about potential photosensitivity with photodynamic therapy during the summer months. Data for 17 patients aged between 4 and 60 years were analysed, with 12 being in the early group and five being in the late group. There was no separate control group. Instead, the late treatment group acted as a control group for the early treatment group and therefore all patients treated in this study received photodynamic therapy. The authors concluded that randomisation appeared not to have resulted in balanced groups and that the power of the study was too low to conclude a beneficial effect of photodynamic therapy in either treatment group.

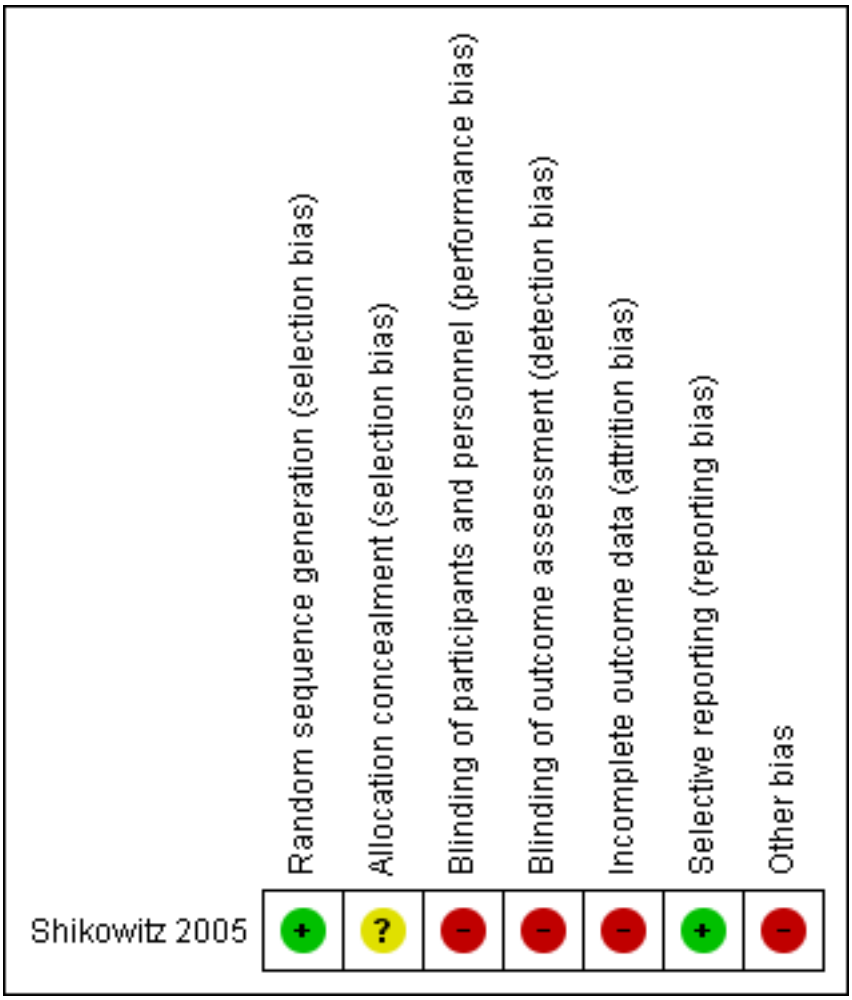
Excluded studies

Eleven studies did not meet the inclusion criteria and were excluded from the review. The studies excluded were not controlled trials (see Characteristics of excluded studies).

Risk of bias in included studies

We assessed the included study for risk of bias (Figure 2).

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Allocation was by a random number table administered by a third party (research nurse) to generate assignment to treatment groups. It was then transmitted to the surgeon personally or by telephone (low risk of bias). It is unclear whether the allocation sequence was concealed (unclear risk of bias).

Blinding

Randomisation was communicated to the surgeon following assignment to treatment groups. Neither surgeons nor patients were blinded before, during or after intervention (high risk of bias).

Incomplete outcome data

Twenty-three patients were initially enrolled in the study and received photodynamic therapy. No data were collected for six patients: five patients withdrew following photodynamic therapy when there was no immediate improvement and one patient relocated and was not followed up for the full follow-up period. The total number of patients included in the analysis is therefore 17, with 12 being in the early intervention group and five in the late intervention group, which also served as a control. Two further patients in the control group withdrew after completion of the 18-month control period (high risk of bias).

Selective reporting

A published protocol was utilised to measure and report outcomes. Withdrawals from the study were reported with reasons stated (low risk of bias).

Other potential sources of bias

The study authors concluded that there were differences in the groups during the time preceding randomisation and that randomisation did not result in balanced groups.

The study was supported by two grants from third parties and no conflict of interest was stated (low risk of bias).

Effects of interventions

See: **Summary of findings for the main comparison**

We had planned to compare photodynamic therapy with or without co-intervention versus control, which would either consist of no intervention or a control intervention. No eligible studies were found for the following comparison groups:

- Photodynamic therapy versus no intervention
- Photodynamic therapy versus inactive control intervention

- Photodynamic therapy versus active control intervention
- Photodynamic therapy plus co-intervention versus no intervention
- Photodynamic therapy plus co-intervention versus inactive control intervention
- Photodynamic therapy plus co-intervention versus co-intervention only (only difference is photodynamic therapy)
- Photodynamic therapy plus co-intervention versus co-intervention only plus inactive co-intervention (only difference is photodynamic therapy)
- Photodynamic therapy plus co-intervention versus co-intervention only plus active co-intervention (only difference is photodynamic therapy)

Photodynamic therapy plus co-intervention versus active control intervention

Primary outcomes

Improvement in symptoms: respiratory distress/dyspnoea, measured by validated questionnaire or lung function testing

Respiratory distress/dyspnoea symptoms were not measured in the included study.

Improvement in symptoms: voice quality, measured by voice quality score or inventory

Voice symptoms were not measured in the included study.

Improvement in quality of life

Quality of life was not measured in the included study.

Recurrence-free interval

The recurrence-free interval was not measured in the included study.

Secondary outcomes

Reduction in mortality

Mortality was not measured in the included study

Reduction in number and/or frequency of surgical interventions and/or time until first relapse requiring surgery

Neither the number/frequency of surgical interventions nor the time until first relapse requiring surgery were measured in the included study.

Reduction in number and/or duration of hospital stay(s)

Hospital stay was not measured in the included study.

Reduction in volume of disease, assessed endoscopically

Data were obtained every three months from enrolment in both groups.

In the early treatment group, five of 12 patients experienced a worsening of disease severity as measured by the papilloma score at endoscopy following photodynamic therapy, which lasted for three to five months. At six to nine months following photodynamic therapy, five patients of 11 with laryngeal disease had no visible papilloma, four patients had improvement (40% to 50% reduction of papilloma) and two patients showed no improvement (less than 25% change). One of 12 patients had tracheal disease only and the results are not reported. Remission was reported to last between three and five years.

The study did not have sufficient power to detect a clinically significant difference, had one been present. Final analyses were performed on pooled treated cohorts (early plus late treatment group). These showed a significant reduction in the laryngeal papilloma score between the initial endoscopy (three months after enrolment) and 12 months following photodynamic therapy (P = 0.007). The trend for change in disease severity for the late treatment group (when this group acted as a control pre-photodynamic therapy) was not significant (P = 0.44).

Adverse effects

Skin photosensitivity is a well-known adverse effect in photodynamic therapy and is usually seen in all patients. Therefore, all patients were instructed to avoid all sun and bright light exposure for two to four weeks. Erythema and swelling of the skin were reported in one patient who was not compliant with these instructions. No further intervention was required. A second patient, a child with severe airway papillomata, developed substantial swelling of the airway a few hours after photodynamic therapy and required intubation to secure the airway for several days.

DISCUSSION

Summary of main results

One randomised controlled trial (RCT) that met our inclusion criteria was identified from the literature search (Shikowitz 2005). Based on the findings from this study we are unable conclude that photodynamic therapy is an effective treatment for recurrent respiratory papillomatosis (RRP). See Summary of findings for the main comparison.

Both the included study and those excluded from this review highlight the difficulty of performing high-power randomised controlled trials in patients with RRP.

RRP is a relatively rare condition. Although the physical, emotional and financial burden of the illness is high, RRP has a relatively low incidence. Derkay and colleagues estimate that it affects about 4.3 per 100,000 children and 1.8 per 100,000 adults in the USA and 3.62 per 100,000 children and 3.94 per 100,000 adults in Western Europe, based on a survey from Denmark (Derkay 2008; Lindeberg 1990). Therefore, there are relatively few patients in any given catchment area of a single treatment centre who may be enrolled in a clinical trial.

There is insufficient evidence from high-quality randomised controlled trials to support the efficacy of photodynamic therapy in the treatment of RRP.

Overall completeness and applicability of evidence

We identified only one study which met our inclusion criteria. This study included all patients with RRP aged two years or older, which encompasses the target patient collective for whom photodynamic therapy might be a viable therapeutic option. There is no evidence from high-quality trials on patients younger than two years with RRP.

In the study included in this review, the main outcome measure was a reduction in papilloma score. The impact of RRP or its treatment on voice and airway or lung function was not reported. Derkay and colleagues have proposed a staging system to assess the severity of RRP, with numeric scores for the extent of the papilloma at specific sites of the aerodigestive tract as well as for functional parameters, resulting in a combined numeric score for extent and function (Derkay 1998). The Abramson and Shikowitz group use their own score (Abramson 1994). Using a unified papilloma score would help to improve the comparability of results and facilitate multicentre trials, which are likely to yield higher power than trials incorporating just one or two centres.

The main symptoms of RRP, voice quality and airway obstruction, are inextricably linked to quality of life and therefore the disease has a major impact on patients. Outcome measures in future studies should therefore include quality of life evaluations as well as functional outcomes, such as lung function and voice quality.

Evidence from uncontrolled case series suggests that photodynamic therapy may be effective in reducing the number of surgeries and the treatment-free interval in patients with RRP (Abrahamson 1992; Abramson 1994; Shikowitz 1998). Photodynamic therapy currently continues to be used in some centres in the USA and Europe to treat RRP based on these findings.

Quality of the evidence

We identified a high risk of bias for blinding of participants and personnel, blinding of outcome assessment and incomplete outcome data in the included study. There is unclear risk of bias for allocation concealment and selective reporting. Six out of 23 participants in the trial dropped out due to perceived inefficacy of the intervention. Furthermore, the included study is insufficiently powered due to the relative rarity of RRP.

Overall the quality of the evidence is very low (Summary of findings for the main comparison).

Potential biases in the review process

We used a comprehensive search strategy in this review (Appendix 1) and updated the search on 27 January 2014. We made every effort to identify potentially eligible studies. No studies were excluded due to language. Where applicable, we retrieved full-text reports of studies in English and other languages and two authors assessed them for eligibility. We identified and screened five reports in German, two in Russian and one in Japanese.

We discussed whether to include the current included study. The study was of low power and randomisation resulted in unbalanced groups. Following discussion with the Cochrane Ear, Nose and Throat Disorders Group, we concluded that it should be included as there was a short period of time (18 months) when the late photodynamic therapy group serves as a control for the early photodynamic therapy group, hence making this a control group.

We contacted the corresponding author (Marc Shikowitz) and were advised that he would help to supply additional data for the 18 months of no photodynamic therapy versus photodynamic therapy. However, he was unable to contribute further data to those already published.

Agreements and disagreements with other studies or reviews

There are currently no other systematic reviews on photodynamic therapy in the treatment of RRP. Two general reviews on RRP have been published (Derkay 2001; Derkay 2008). These review surgical management, which has been the mainstay of treatment, as well as a adjuvant treatment modalities, with an emphasis on interferon and antiviral treatment (Derkay 2001). In the later review, photodynamic therapy is discussed and two studies by Shikowitz et al are acknowledged (Derkay 2008). We screened both of these studies for this review, with one of them being included.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence from high-quality randomised controlled trials that photodynamic therapy alters the course of disease or provides an added benefit to surgery in recurrent respiratory papillomatosis.

Implications for research

Multicentre randomised controlled trials, with appropriate sample sizes and long-term follow-up, would be required to evaluate whether photodynamic therapy is of significant benefit in the management of recurrent respiratory papillomatosis. Trials should include outcome measures such as improvement in symptoms (respiratory function and voice quality, using validated questionnaires or objective measurements) and quality of life measurements.

Many surgeons now use a powered microdebrider, rather than cold steel instrumentation or laser, which allows more precise removal of lesions and leads to less scarring and a lower risk of adhesions or stenosis (Imaizumi 2012; Pasquale 2003). This development may have an impact on further research into adjuvant treatments for RRP as there may be a decreasing need for adjuvant therapies in the future, except in the case of disseminated or advanced disease.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Shikowitz 2005

Methods	**Allocation:** randomised controlled trial
	Design: parallel-arm study

Shikowitz 2005 *(Continued)*

Participants	**Number:** 23 patients **Age:** patients aged 4 years to 60 years **Gender:** 13 male and 4 female **Setting:** day-case surgery at 2 centres in the state of New York, USA **Eligibility criteria:** older than 2 years with multiple RRP recurrences requiring surgery 3 or more times per year and/or tracheobronchial involvement **Exclusion criteria:** none reported **Baseline characteristics:** patients with RRP requiring surgery 3 or more times per year and/or tracheobronchial involvement
Interventions	PDT with 0.15 mg/kg intravenous m-THPC, followed by upper airway endoscopy 6 days after m-THPC administration and 652 nm diode laser activating light (80 to 100 J for adults and 60 to 80 J for children, depending on plasma concentration of m-THPC at the time of PDT) Early treatment group (intervention): PDT 6 months after enrolment; n = 12 Late treatment group (control): PDT 18 months after enrolment; n = 5 The late treatment group (who had no PDT until 18 months after enrolment) served as a control group for the early treatment group between time point 6 months and 18 months after enrolment **Use of additional interventions:** surgical removal of papillomata used in either group when clinically required
Outcomes	**Primary outcome:** None of this review's primary outcomes were measured in this study **Secondary outcomes:** Volume of disease, utilising a papilloma score at the time of enrolment, at the time of PDT (6 months for intervention group and 18 months for control group), then every 3 months for 18 months following intervention, combined with surgical removal of papilloma where required. The primary unit of analysis was the participant's average papilloma score per day. The change in percentage score between time of randomisation and initial surgery and after PDT was analysed and given as a percentage Other parameters measured were plasma concentration of m-THPC, presence of HPV DNA in clinically normal biopsies following PDT and expression of interferon-gamma and interleukin-10 messenger RNA cytokines as a measure of host immune response
Notes	The late intervention group served as a control group for the early intervention group for 18 months after enrolment/for 12 months from the date the early treatment group received PDT, until patients in the control group also received PDT

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table to generate assignment to treatment groups
Allocation concealment (selection bias)	Unclear risk	"... the randomizations were transmitted to the surgeon by the nurse clinician either personally or by telephone..."
Blinding of participants and personnel (performance bias)	High risk	No blinding of surgeons or patients

Shikowitz 2005 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	17 out of 23 patients completed the trial
Selective reporting (reporting bias)	Low risk	A published protocol was used and adhered to and withdrawals were reported
Other bias	High risk	The study authors concluded that there were differences in the groups during the time preceding randomisation and that randomisation did not result in balanced groups. The study was supported by 2 grants from third parties and no conflict of interest was stated

HPV: human papillomavirus
m-THPC: meso-tetra (hydroxyphenyl) chlorin
PDT: photodynamic therapy
RNA: ribonucleic acid
RRP: recurrent respiratory papillomatosis

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abrahamson 1992	ALLOCATION: This study is not a RCT: all patients were treated with PDT; there is no control group
Abramson 1994	ALLOCATION: This study is not a RCT: all patients were treated with PDT; there is no control group
Feyh 1993	ALLOCATION: This study is not a RCT: a subgroup of patients had RRP; all patients were treated with PDT; there is no control group.
Feyh 1995	ALLOCATION: This study is not a RCT: all patients were treated with PDT; there is no control group This report is a duplicate in English of a study published previously in German
Leunig 2000	ALLOCATION: This study is not a RCT: all patients were treated with PDT; there is no control group
Lippert 2002	ALLOCATION: This study is not a RCT: all patients were treated with PDT; there is no control group
Ronn 1996	ALLOCATION: This study is not a RCT: all patients were treated with PDT; there is no control group
Shikowitz 1998	ALLOCATION: This study is not a RCT: although this is a controlled trial, allocation to treatment and control groups was by patient preference, not randomisation
Sokolov 2007	ALLOCATION:

Study	Reason for exclusion
	This study is not a RCT: all patients were treated with PDT; there is no control group
Sokolov 2010	ALLOCATION: This study is not a RCT: all patients were treated with PDT; there is no control group. Patients do not have RRP: malignancies and pre-malignancies were treated with PDT in this study

PDT: photodynamic therapy
RCT: randomised controlled trial
RRP: recurrent respiratory papillomatosis

APPENDICES

Appendix 1. Search strategies

CENTRAL	PubMed	EMBASE (Ovid)
#1 MeSH descriptor Papilloma explode all trees #2 MeSH descriptor Papillomavirus Infections explode all trees #3 (papilloma* OR wart* OR hpv) #4 (#1 OR #2 OR #3) #5 laryn* OR trache* OR pharynx* OR vocal NEXT cord* OR vocal NEXT fold* OR voice NEXT box OR throat OR respirat* OR airway OR aerodigesti* OR bronchial #6 MeSH descriptor Laryngeal Neoplasms explode all trees #7 MeSH descriptor Respiratory Tract Neoplasms explode all trees #8 (#5 OR #6 OR #7) #9 (#8 AND #4) #10 laryngeal NEXT papilloma* OR recurrent AND papilloma* OR RRP OR RLP OR JORRP #11 MeSH descriptor Photochemotherapy explode all trees #12 photodynamic OR photochemo* OR photosensiti* OR phototherapy OR PDT #13 meso* OR m-THPC OR dihematoporphyrinether OR DHE OR aminolevulinic OR ALA #14 (#11 OR #12 OR #13) #15 (#9 OR #10) #16 (#14 AND #15)	#1 “PAPILLOMA” [MeSH] OR “PAPILLOMAVIRUS INFECTIONS” [MeSH] OR papilloma* OR wart* OR hpv #2 laryn* OR trache* OR pharynx* OR “vocal cord*” OR “vocal cords” OR “vocal fold” OR “vocal folds” OR “voice box” OR throat OR respirat* OR airway OR aerodigesti* OR bronchial* #3 “LARYNGEAL NEOPLASMS” [MeSH] OR “RESPIRATORY TRACT NEOPLASMS” #4 #2 OR #3 #5 #1 AND #4 #6 (laryngeal AND papilloma*) OR (recurrent AND papilloma*) OR RRP OR RLP OR JORRP #7 #5 OR #6 #8 “PHOTOCHEMOTHERAPY” [MeSH] OR photodynamic OR photochemo* OR photosensiti* OR phototherapy OR PDT #9 meso* OR m-THPC OR dihematoporphyrinether OR DHE OR aminolevulinic OR ALA #10 #8 OR #9 #11 #7 AND #12	1 exp papilloma/ or exp papilloma virus/ 2 (laryn* or trache* or pharynx* or (vocal adj cord*) or (vocal adj fold*) or (voice adj box) or throat or respirat* or airway or aerodigesti* or bronchial).tw. 3 exp larynx tumor/ 4 2 or 3 5 1 and 4 6 ((laryngeal and papilloma*) or (recurrent and papilloma*) or RRP or RLP or JORRP).tw. 7 5 or 6 8 photodynamic therapy/ or exp photodynamics/ 9 (photodynamic or photochemo* or photosensiti* or phototherapy or PDT).tw. 10 (meso* or m-THPC or dihematoporphyrinether or DHE or aminolevulinic or ALA).tw. 11 8 or 9 or 10 12 7 and 11

(Continued)

Web of Science (Web of Knowledge)	CINAHL (EBSCO)	ICTRP
#1 TS=(papilloma* OR wart* OR hpv) #2 TS=(laryn* OR trache* OR pharynx* OR (vocal adj cord*) OR (vocal adj fold*) OR (voice adj box) OR throat OR respirat* OR airway OR aerodigesti* OR bronchial) #3 #2 AND #1 #4 TS=((recurrent AND papilloma*) OR RRP OR RLP OR JORRP) #5 #4 OR #3 #6 TS=(photodynamic OR photochemo* OR photosensiti* OR phototherapy OR PDT) #7 TS=(meso* OR m-THPC OR dihematoporphyrinether OR DHE OR aminolevulinic OR ALA) #8 #7 OR #6 #9 #8 AND #5	S1 (MH "Papilloma") S2 TX (papilloma* OR wart* OR hpv) S3 S1 or S2 S4 TX (laryn* or trache* or pharynx* or (vocal adj cord*) or (vocal adj fold*) or (voice adj box) or throat or respirat* or airway or aerodigesti* or bronchial) S5 (MH "Laryngeal Neoplasms") S6 (MH "Respiratory Tract Neoplasms+") S7 S4 or S5 or S6 S8 S3 and S7 S9 TX ((laryngeal and papilloma*) or (recurrent and papilloma*) or RRP or RLP or JORRP) S10 S8 or S9 S11 (MH "Photodynamic Therapy") S12 (photodynamic or photochemo* or photosensiti* or phototherapy or PDT) S13 S11 or S12 S14 S10 and S13	respiratory AND papilloma* OR laryn* AND papilloma* OR trache* AND papilloma* OR respiratory AND wart* OR laryn* AND wart* OR trache* AND wart* OR respiratory AND hpv OR laryn* AND hpv OR trache* AND hpv

CONTRIBUTIONS OF AUTHORS

A Lieder: title registration; drafting protocol; additional searching for studies; initial screening and study selection; quality assessment; data extraction and analysis; gathering missing data, drafting and revision of the review manuscript.

M Khan: drafting protocol; initial screening and study selection; quality assessment; data extraction.

BM Lippert: content expertise; identification of studies; resolution of disagreements and discussion, revision of the review manuscript.

DECLARATIONS OF INTEREST

The authors declare that there are no competing interests.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We included a 'Summary of findings' table following the recommendations in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

Mesoporphyrins [*therapeutic use]; Papillomavirus Infections [*drug therapy]; Photochemotherapy [adverse effects] [*methods]; Photosensitizing Agents [*therapeutic use]; Randomized Controlled Trials as Topic; Recurrence; Respiratory Tract Infections [*drug therapy]

MeSH check words

Adult; Humans