NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of collagen injection for vocal cord augmentation

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in December 2004.

Procedure name

Collagen injection into vocal cord / fold.

Specialty societies

- British Association of Otolaryngologists.
- British Voice Association.

Description

Indications

Glottic insufficiency is a condition that leaves patients with phonatory compromise in both voice intensity and frequency, which may be secondary to vocal fold (cord) scarring, atrophy, or paresis. Severe vocal difficulty can considerably impair communication. Vocal fold paresis - where the nerves that control the muscles acting on the vocal fold fail - may be idiopathic or due to a iatrogenic cause. This may affect either of the vocal folds or may be bilateral, and is the most common reason for performing this procedure.

Current treatment and alternatives

Conservative management by voice therapy (training) may be beneficial if vocal paresis affects muscle groups in the throat which can be developed through vocal exercise. Surgical approaches are used to reposition or reshape the vocal fold and may involve implanting a physical device to better position the vocal fold. Autogenous fat, Teflon and silicon can be injected to improve vocal fold function of these autogenous fat is generally well tolerated, Teflon and silicon, however, may (rarely) produce complications because of sensitivity reactions to the materials used.

What the procedure involves:

The collagen is injected either transorally or transcutaneously from below the vocal fold using a laryngeal needle. The exact placement of collagen varies depending on the patient's pathology. The procedure can be carried out with local anaesthesia, and may not require admission. A variety of collagen products have been used in research studies, for example biochemical cross-linked products and purified bovine collagen. Patients who are selected for therapy commonly undergo a skin sensitivity test. Antibiotic prophylaxis may be given

Efficacy

In a case series of 45 patients with glottic insufficiency in whom other forms of treatment were considered unsuitable, collagen injection improved maximum achieved voice intensity by 2.91 dB ($p<0.026$) at 12 months following the procedure, however voice intensity during normal speech did not improve significantly from baseline scores(1).

Voice intensity and phonation time (the maximum time a sound can be sustained with one breath) was found to improve significantly following collagen injection in a mixed sample of 27 with vocal cord paralysis or glottic insufficiency following laryngeal surgery. Also all 27 patients reported improvement in at least one subjective voice assessment parameter up to 16 weeks post collagen injection(2).

One small case series of 18 patients with electromyographically confirmed vocal cord paralysis who were injected with purified bovine collagen found good improvement in dysphonia score compared to baseline in 95% of patients (17/18) at 6.5 months after treatment(3). In the same study objective measurement of voice function at 3 days post injection an improvement was found in maximum vocal time achieved (9 Vs 6 seconds) and also an improved phonatory quotient (341 Vs 682 ml/s). IN a longer term follow up of patients in this study to 3 years 83% (5/6) maintained good results in terms of subjective voice assessment(4). For the 4 patients available for objective voice assessment the maximum phonation time was still better (12 Vs 4 seconds) and phonatory quotient remained improved compared to baseline score (352 Vs 649 ml/s).

Safety

Among 27 patients treated with collagen injection in a case series, short term adverse events of transient oedema and immediate decrease in voice quality were reported in 4% (1/27) of cases(2).

Two case series(1;3) with a total of 63 patients undergoing collagen injection in to the vocal fold found no serious adverse events up to 12 months. In six of these patients followed up for 3 years there were no complications such as seromas, granuloma formation or migration of injected collagen(4).

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to collagen injection for vocal cord augmentation. Searches were conducted via the following databases, covering the period from their commencement to 11 August 2004: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and Science Citation Index. Trial registries and the Internet were also searched. No language restriction was applied to the searches.

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with vocal cord paralysis either unilateral or secondary to trauma or surgery
Intervention/test	Injection of collagen (bovine or cross matched) into the vocal cord or fold.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on four reports from three distinct case series.

Existing reviews on this procedure

No existing systematic reviews or evidence-based guidelines on this topic were located during literature searching.

Table 1 Summary of key efficacy and safety findings on selective internal radiation therapy

Abbreviation used:			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Remacle M (1986)(3) Case series Belgium n = 18 17 patients with paralysis of vocal cord, 1 patient with atrophy of vocal cord Age = 57 years, male = 94%, indication for intervention being dystonia = 100% Electromyography confirmed vocal cord paralysis Injection of 1.5 cc into Reinke's space Purified bovine collagen Mean follow-up 6.5 months, by laryngoscopic examination, stroboscopic evaluation, and objective phonatory assessment	**Subjective voice assessment** Both shortly after injection, and in medium term (to a mean follow-up of 6.5 months) Dysphonia Good improvement: 78% (14/18) post injection; 95% (13/14) medium term Fair improvement: 22% (4/18) post injection; 5% (1/14) medium term **Objective phonatory measurement** Changes in scores from baseline to 3 days post injection in 15 cases are reported here. Longer term outcome assessment had high attrition rates Parameter: baseline; 3 days Max. vocalic time (secs): 5.7 (3.5 to 12); 8.6 (4 to 18) Phonatory quotient (ml/second): 682 (206 to 1200); 341 (196 to 561) Mean flow rate (ml/second): 636 (269 to 1212); 286 (182 to 423) (Mean scores and range)	**Intervention complications** No complications, such as inflammation of the vocal cord were recorded in any patient **Collagen stability** No incidence of the formation of granuloma at the injection site, or migration of the product into the sub-glottis.	Assessment method for subjective voice evaluation is not stated. Objective vocal scores depend on the quality of the lungs and the available volume of expiratory air. Longer-term studies to 3 years are needed to compare efficacy with that of other injection agents.

Abbreviation used:			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Ford JM (1986)(2) Case series USA n = 27 18 patients with vocal cord paralysis or paresis 9 patients with glottic insufficiency after laryngeal surgery All patients had glottal incompetence and concomitant voice problems Age = 51 years, male = 74%, previous treatment with Teflon=19% Zyderm II collagen implant into the vocalis muscle, vocal ligament or mucosal planes, or - where vocal fold atrophy was present - injection at the level of the lamina propria Assessment with videostoboscopic, aerodynamic and acoustic recordings, and perceptual judgement of voice quality Mean follow-up 16 weeks	**Subjective voice assessment** Subjects used a 5-point scale to self-rate voice loudness, quality, pitch, fatiguability, and clarity All 27 patients reported improvement in at least one item. Most patients improved on several parameters. Some patients improved by 5 points, some by only 1. Fatiguability worsened in the subgroup of patients who had previously been treated with Teflon, which was removed during the collagen procedure **Objective phonatory measurement** Across the whole study sample there were statistically significant improvements in voice intensity (dB) and phonation time (secs) compared to baseline score ($p < 0.05$ for both) Improved airflow following the collagen injection was recorded ($p < 0.01$). For both of these comparisons absolute figures are available for each indication subgroup	**Adverse outcomes** No severe complications following injection in 27 cases 4% (1/27) suffered transient oedema 4% (1/27) reported immediate decrease in vocal quality post-intervention due to over injection of material causing focal ballooning 4% (1/27) were startled by elevated voice pitch, which was corrected with voice therapy	Baseline scores determined by repeated measurement to reduce variation in results. Data from subjects over several months post treatment show substantial changes in efficacy over time. In some cases there is continued improvement, while in others vocal function deteriorates. Concomitant vocal training at 1 week may have a vital effect on efficacy outcomes by adjusting patients to the altered glottic anatomy. Short-term follow-up only. Injected material is resorbed at various rates in the study population.

Abbreviation used:			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Remacle M (1989)(4) Case series Belgium Same population as for Remacle (1986) with long term outcomes reported Follow-up to a minimum 3 yrs	**Long term efficacy** Of the 14 patients from initial sample, 7 died (6 from underlying broncho-pulmonary cancer) 1 patient was lost to follow up. This left 4 patients available for objective voice function testing, and 2 more available for telephone interview, two of these patients had undergone re-injection of collagen 83% of patients (5/6) maintained stable results in terms of subjective voice assessment For the 4 patients assessed objectively the efficacy of the intervention remained good, although no statistical analysis was undertaken Baseline 3 yrs Max. phonation time (seconds) 4.25 12.25 Phonatory quotient (ml/second) 649 352 Mean values	**Adverse events** No complications that are common in alternative treatment options - such as seromas, granuloma formation, sub glottic or distal migration, or tumour mimesis - were reported	High attrition rate. Only 4 of 14 patients available for full laboratory assessment of vocal function. Some patients had received repeat collagen injection.
Ford JM (1993)(1) Case series USA n = 45 Patients with glottic insufficiency for whom other forms of treatment were considered inadequate or contraindicated Age = 58 years, male = 44% Following a skin test, Zyplast collagen was implanted into the vocalis muscle, vocal ligament, or mucosal planes, or - where vocal fold atrophy was present - at the level of the lamina propria	**Self evaluation** No patients reported worse voice function during follow–up, except for one patient who had a seriously scarred larynx at baseline and seemed to worsen for several weeks before improvement was noted One patient had spasmodic dysphonia and was excluded from assessment, and 4 patients were aphonic at baseline and were excluded from lab assessment **Perceptual ratings** Patients were assessed by recording their reading of a standard sentence, and rated as having either a deterioration in voice -1, remained the same 0, or improved +1. For 39% (17/44) of patients the scores remained unchanged. Overall the mean score change from baseline was 0.477 (SD1.486) (p = 0.039) **Acoustic measures**	There were no serious complications reported during the study, including airway obstruction, or hypersensitivity to the injection	Scales for self assessment and perceptual judgements not validated. A carefully selected series of patients not suitable for other therapy. Small sample size makes comparison of efficacy between indications difficult. 18 patients received multiple injections, these were not analysed separately. No definition given for unsuitability for other treatment options..

Abbreviation used:

Study details	Key efficacy findings	Key safety findings	Comments
Evaluation of voice function at baseline and follow-up by subjective self assessment by questionnaire, perceptual judgement by independent judges (using 10% duplicate assessment to test reliability), acoustic and aerodynamic measures, lab assessment, and vocal fold vibration by videostroboscopy Follow-up 12 months	<table><tr><th>Parameter</th><th>Mean change</th><th>SD</th><th>P value</th></tr><tr><td>Intensity max (dB)</td><td>2.91</td><td>8.26</td><td>0.026</td></tr><tr><td>Intensity normal (dB)</td><td>0.86</td><td>5.70</td><td>0.321</td></tr><tr><td>Frequency range</td><td>3.03</td><td>9.01</td><td>0.040</td></tr></table> There was considerable individual variation in scores and some difference between pathological subgroups. However, these were not statistically significant		

Validity and generalisability of the studies

Case series are generally more than 10 years old and technique may have advanced in the interim.

There is little long-term follow up of patients, and stability of collagen material is not fully documented.

Many patients in the studies have had multiple treatments and it is not clear whether outcomes are compared with baseline or with scores before their final treatment.

There are few data on the comparative efficacy in patients following trauma or surgery and those with idiopathic paresi /paralysis.

Voice function scores (both objective and subjective) may vary over time and baseline measurements are not always repeated for consistency.

The exact site and depth of injection of collagen differs between studies.

Specialist advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

- Most advisors commented that injected collagen may be absorbed over time and may require replacement in the long term

- The effect of collagen injection on the elastic properties of the larynx are not necessarily directly related to improvement in voce quality

- Over injection of collagen may cause haematoma or oedema

- There are theoretical safety concerns regarding the use of bovine collagen in terms of possible vCJD infection or allergic reaction, the latter can be averted by use of a skin sensitivity test prior to the procedure

- Selection of suitable patients can be achieved through MDT review of laboratory voice function assessment

- No specific training is required to undertake this procedure over basic experience of ENT equipment.

Issues for consideration by IPAC

- Long-term benefit has to be weighed against high mortality in the population with advanced cancer.

- The concomitant use of vocal training folowing injection may be influential in providing positive outcomes.

- Cross linked or autologous collagen products may be better tolerated than bovine products and may also prove more durable.

References

(1) Ford CN, Bless DM. Selected problems treated by vocal fold injection of collagen. American Journal of Otolaryngology 1993; 14(4):257-261.

(2) Ford CN, Bless DM. A preliminary study of injectable collagen in human vocal fold augmentation. Otolaryngology - Head & Neck Surgery 1986; 94(1):104-112.

(3) Remacle M, Clerin M, Dubois P, Ryckaert M, Bertrand B, Hamoir M. Exploration of glottic function before and after injection of collagen for rehabilitation of the vocal cord. Acta Oto-Rhino-Laryngologica Belgica 1986; 40(2):405-420.

(4) Remacle M, Marbaix E, Hamoir M, Declaye X, Van Den EJ. Inital long-term results of collagen injection for vocal and laryngeal rehabilitation. Archives of Oto-Rhino-Laryngology Vol 246(5)()(pp 403-406), 1989 1989;(5):403-406.

Appendix A: Additional papers on selective international radiation therapy not included in the summary tables

Article title	Number of patients/follow-up	Comments	Direction of conclusions
Ford CN, Bless DM. Clinical experience with injectable collagen for vocal fold augmentation. *Laryngoscope* Vol 96(8)()(pp 863-869), 1986 1986;(8):863-9.	n=54 2 years	Excluded patients who didn't return for follow-up	Responses vary at 1 week, stabilise at 3 months and slightly decline at 1 year. Rehabilitation better where unilateral fold paralysis
Havas T, Priestley J. The management of unilateral vocal fold paralysis: The Sydney Voice Clinic experience. *Australian Journal of Otolaryngology* Vol 2(4)()(pp 363-368), 1996 1996;(4):363-8.	n=64 16 months	Only one patient treated with collagen	Injection techniques have been modified with experience. Voice outcomes more important than anatomical normality
Hoffman H, McCabe D, McCulloch T, Jin SM, Karnell M. Laryngeal collagen injection as an adjunct to medialization laryngoplasty. *Laryngoscope* 2002; 112(8:Pt 1):t-13.	n=7 7 months	Small study cohort	An office based approach. Subjective and objective assessment measures demonstrate improvement post injection
Remacle MJ, Marbaix E, Bertrand BM. The value of injectable collagen in vocal and glottic rehabilitation. *Archives of Oto-Rhino-Laryngology* 1986; 243(4):233-7.	n=14 up to 12 months	Same study cohort as for Remacle (1986)	All patients showed improved dysphonia with collagen injection which was well tolerated.

Appendix B: Literature search for collagen injection for vocal cord augmentation

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in EMBASE, Current Contents, PredMedline and all EMB databases.

For all other databases a simple search strategy using the key words in the title was employed.

#	Search History	Results	Display
1	Vocal Cords/ Details	5856	Display
2	(vocal adj cord$).tw. Details	5502	Display
3	(vocal adj fold$).tw. Details	2973	Display
4	1 or 2 or 3 Details	10624	Display
5	paraly$.tw. Details	35921	Display
6	paresis$.tw. Details	6545	Display
7	plegia$.tw. Details	77	Display
8	palsy.tw. Details	25829	Display
9	palsies.tw. Details	3299	Display
10	or/5-9 Details	67198	Display
11	4 and 10 Details	2783	Display
12	VOCAL CORD PARALYSIS/ Details	4006	Display
13	11 or 12 Details	4767	Display
14	exp Collagen/ Details	86787	Display
15	Collag$.tw. Details	126981	Display
16	14 or 15 Details	146905	Display
17	13 and 16 Details	103	Display