

Role of Gene Therapy in the Management of Unilateral Vocal Fold Paralysis

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1. Introduction

Vocal cord paralysis can occur as a result of injury to the recurrent laryngeal nerve (RLN). Possible causes include iatrogenic surgical injury (cardiac, thoracic, neck), neoplasm (e.g. thyroid, esophagus, lung) or neurological disease. Injury to the RLN results in vocal cord paresis or paralysis. Poor or absent movement of one or both vocal folds causes difficulties with voice, swallowing or breathing. This can have a substantial negative effect on quality of life due to poor vocal function, aspiration, and upper airway obstruction in the rare event of bilateral RLN injury.

2. Anatomy of the recurrent laryngeal nerve

Injury to the RLN can occur at any point along the course of the nerve, which spans the neck and thorax. The RLN is a branch of the vagus nerve, and has an extensive and complex anatomical course, beginning at the brainstem, coursing through the skull base, within the carotid sheath in the neck, into the thorax, looping around the aortic arch (left RLN), around the subclavian artery (right RLN), within the tracheoesophageal groove, posteromedial to the thyroid gland, and enters the larynx at the posteroinferior border of the cricoid cartilage. The RLN provides motor supply to the thyroarytenoid muscle, posterior cricoarytenoid muscle, lateral cricoarytenoid muscle, and interarytenoid muscles. It also provides sensory supply to the glottis and infraglottic larynx.

3. Current management options for unilateral vocal cord paralysis

Standard options for management of unilateral vocal cord paralysis include observation, voice and swallowing therapy, and surgery.

4. Observation

Patients sometimes exhibit variable clinical improvement with expectant management. This can be due to (i) spontaneous nerve regeneration, or (ii) natural compensation for glottic insufficiency by strengthening of the contralateral vocal cord.

5. Voice and swallowing therapy

A referral to an experienced speech language pathologist is commonly employed in cases of severe functional deficit where patients are reluctant or unfit to pursue surgery. Voice and swallowing rehabilitation has been shown to be effective, especially in motivated patients.

6. Surgery

Medialization of the paralyzed vocal cord aims to close the glottic gap, resulting in improvement in voice and aspiration. Specific procedures can be classified into endolaryngeal and extralaryngeal. Endolaryngeal procedures include injection laryngoplasty, whereby a 'filler' substance is injected into the paraglottic space, either percutaneously or endoscopically. Percutaneous approaches are performed in the clinic as an office-based procedure, and can be done safely under endoscopic guidance with local anaesthesia transorally, through the thyrohyoid membrane, through the thyroid cartilage, or most commonly, through the cricothyroid membrane. "Filler" substances commonly employed include calcium hydroxyapatite, collagen, and autologous fat. Extralaryngeal procedures include medialization laryngoplasty (thyroplasty), arytenoid adduction, and cricothyroid subluxation with adduction arytenopexy. The most commonly performed extralaryngeal procedure is the medialization thyroplasty. This is done in the operating room with IV sedation. The laryngeal framework is approached transcervically, and an alloplastic implant (such as Gortex™ or silastic) is inserted into the paraglottic space after drilling a window through the thyroid cartilage. This operation can be safely performed as an outpatient in selected patients (Zhao et al., 2010). Although implants can be hand-carved, contemporary thyroplasty systems include fully or partially pre-fabricated implants with gender-specific sizes and templates, for improved technical precision.

7. Pitfalls and shortcomings of current therapies

Although current therapies have been shown to be clinically effective, they represent static solutions to a dynamic problem. Physiologic vocal cord function is not actually restored. The ability to restore physiologic vocal cord movement depends upon developing strategies to maintain survival of injured or vulnerable neurons and to stimulate axonal regeneration to appropriate laryngeal muscles (Hogikyan et al. 2001, Rubin et al. 2003).

8. Nerve regeneration

Spontaneous natural nerve recovery can occur, but axon regrowth may fail to reach the laryngeal muscles, or fail to reinnervate the correct muscles (Crumley et al. 2000). Non-selective reinnervation of adductor and abductor laryngeal muscles results in synkinesis, which explains the variable clinical outcomes observed with expectant management.

It is known that neurotrophic and neuroprotective growth factors can prevent nerve degeneration following injury. Administration of these growth factors through the central nervous system (CNS) is an appealing strategy. However, technical access to these neurons is challenging, and direct injection is ineffective, since trophic factors diffuse poorly, and can cause injury to adjacent neuronal structures. A novel and innovative approach that is minimally invasive and avoids systemic side effects is remote delivery utilizing a viral vector, and forms the fundamental basis of the emerging evidence from investigations into the potential role of gene therapy for treatment of recurrent laryngeal nerve injury.

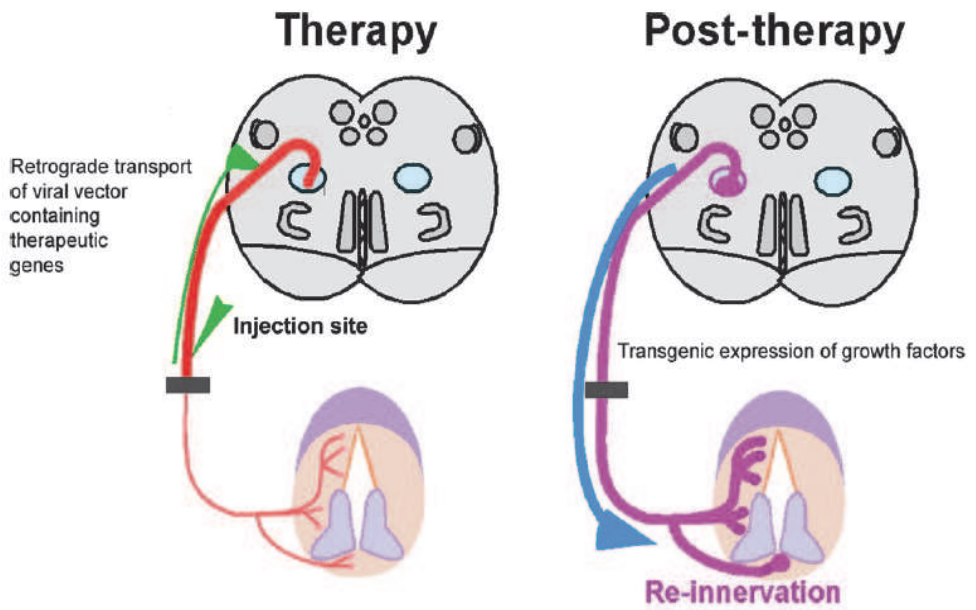
9. Gene therapy – a promising novel strategy for treatment of RLN injury

The remote delivery of genes encoding therapeutic growth factors to the CNS is an attractive management strategy, because it avoids the potential pitfalls of direct CNS injection (into the brainstem or spinal cord) and systemic administration. In this approach, viral vectors can be injected into the peripheral nervous system and be transported in a retrograde fashion to the CNS (Boulis et al. 1999, Rubin et al. 2001). Several viral vectors have been described for *in vivo* gene transfer in the nervous system, including herpes simplex virus, retroviruses, adenovirus, and adeno-associated virus (AAV). Contemporary bench techniques can impact virus attenuation, thereby preventing the negative consequences of local proliferation, and allow the addition of potentially therapeutic genes.

Previous research by our group has shown that an AAV vector, remotely injected into the RLN, travels in a retrograde fashion to the rat brainstem (Rubin et al. 2001) and that injection of an adenoviral vector into a crushed RLN added no additional injury compared with crush alone (Shiotani et al. 1999).

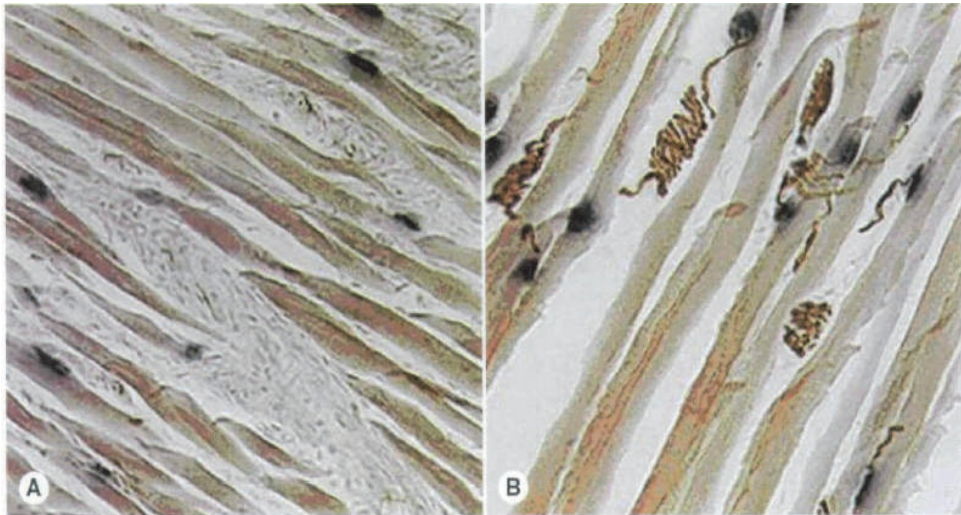
An experimental model of RLN injury for the study of viral gene therapy has been previously described (Fung et al., 2008, Figure 1). In this model, a standardized crush injury was induced to the RLN. Immediately following crush, there was a dramatic, measurable decrease in nerve-endplate contact percentage, and spontaneous recovery was observed by three weeks post-injury. Recovery was confirmed both endoscopically as well as histologically by determining a high nerve-endplate contact percentage. Nerve-endplate contact was quantified by a rigorous method of evaluation of immunohistochemically stained rat larynges for neurofilament and motor endplates. We showed that this method reliably quantified the anatomical integrity of neuromuscular connections in laryngeal muscle.

There are promising results from a study (Sabowski et al., 2009) investigating the effects of remote administration of an engineered zinc-finger protein transcription factor, Ad-32Ep65-Flag (Ad-p65). This factor has been found to induce expression of vascular endothelial growth factor (VEGF; also called VEGF-A). VEGF has well known neuroprotective effects. Subsequent work demonstrated that remote injection of Ad-p65 after RLN crush accelerated the return of vocal fold mobility and the percentage of nerve-endplate contacts in the thyroarytenoid muscle. Similar results have been described with adenoviral GDNF gene transfer (Araki et al., 2006). This study observed faster motor nerve conduction velocity of the RLN and quicker recovery rate of vocal fold movement following gene transfer.



*reproduced from Fung et al. (2008)

Fig. 1.



Reproduced from Fung et al. (2008)

Fig. 2. (A) Denervation, as evidenced by low neuron-motor endplate contact percentage, following crush injury.

(B) Reinnervation, as evidence by high neuron-motor endplate contact percentage, following 3 weeks of recovery.

10. Conclusion

Gene therapy is a promising methodology that may enhance our ability to minimize nerve injury while maximizing functional outcome. Research using this model to investigate the potential therapeutic role of viral gene therapy for the treatment of recurrent laryngeal nerve injury is ongoing.

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The aim of our book is to provide a detailed discussion of gene therapy application in human diseases. The book brings together major approaches: (1) Gene therapy in blood and vascular system, (2) Gene therapy in orthopedics, (3) Gene therapy in genitourinary system, (4) Gene therapy in other diseases. This source will make clinicians and researchers comfortable with the potential and problems of gene therapy application.

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