A Comparison of Conventional, Revascularized and Bioengineered Methods of Recurrent Laryngeal Nerve Reconstruction

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ABSTRACT

Importance:
Damage to the recurrent laryngeal nerve (RLN) is highly detrimental to voice, swallow and cough. Nerve sacrifice is often necessary for thyroid or other cervical malignancies. The optimal reconstitution of this nerve after injury is unknown.

Materials and Methods:
An established canine model of RLN injury was utilized. Laryngeal adductor pressures (LAPs) were measured with a pressure transducer balloon pre-injury and 6 months post-injury via electrical stimulation of the RLN. The recurrent laryngeal nerve was reconstructed after simple transection directly or with two types of nerve conduits (silastic and neurotube). The nerve conduits were each 2 cm long and had 0.5 cm of the transected nerve endings loaded into each side, which permitted a 1 cm gap. The silastic conduit reconstructed with an empty carrier (n=4), a fibrin-embedded carrier (n=4), a fibrin-embedded glial cell-derived neurotrophic factor carrier (n=8) or a fibrin-embedded neurotrophin-3 carrier (n=8). The neurotube conduit utilized a woven polyglycolic acid construct (n=11). Values were compared with transection of the RLN and direct neurorrhaphy (n=16). For reconstruction of the RLN with an intervening graft, a 5 cm segment of RLN was removed. Revascularized nerve grafts (5 cm, n=4) were harvested from the saphenous nerve, artery and vein with microvascular anastamosis performed to the cranial thyroid artery and internal jugular vein. Conventional cable grafts (5 cm, n=6) were also harvested from the saphenous nerve. As a comparison group, a section of RLN was removed and anastomosed in reverse configuration (2 cm, n=8). Acellular nerve allografts (5 cm, n=6) were harvested from canine saphenous nerves, engineered via established protocols and implanted into research subjects.

Results:
Simple RLN transection with direct neurorrhaphy provided 55.5% (± 12.5%) recovery of baseline LAPs. Reverse autografts provided 60.8% (± 27.5%) recovery of the baseline LAPs. Revascularized and conventional nerve grafts provided a range of recoveries of LAPs. All revascularized nerve grafts were noted to have patent blood supply at canine sacrifice. Two of eleven neurotube reconstructions provided a measurable LAP with an average recovery of 37.1% of baseline. Reconstruction with an acellular nerve graft or a neural conduit in any condition provided no measurable LAP recovery.

Conclusions:
Conventional nerve grafting provided equivalent recovery of laryngeal adductor pressures following recurrent laryngeal nerve repair as to a simple repair or a reverse autograft. Revascularized nerve grafts did not appear to provide additional recovery benefit. The use of bioengineered acellular nerve grafts and nerve conduits for reconstruction resulted in poor recovery of recurrent laryngeal nerve function.

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INTRODUCTION

Although there is some inherent capability for nerves to regenerate, recovery after damage to a peripheral nerve is frequently unpredictable and can result in a poor outcome. When a nerve is completely transected, the distal and proximal stump can often be directly repaired via microsurgical suturing. However, in many cases this primary nerve repair may not be feasible and a bridging component of tissue is used to provide a tension free anastamosis (Siemionow 2009). Situations where this typically occurs are after trauma or during a cancer operation. When selecting a graft, surgeons usually choose to utilize an autologous nerve graft harvested from the patient's body. The use of an autograft can be limited by size mismatch among the nerve tissues and also by a lack of sufficient donor sites (Burnett 2004, Schmidt 2003). Several of these types of grafts exist; including skeletonized cable grafts, acellular nerve graft substitutes or vascularized nerve grafts. When these nerves are repaired under tension, there is almost always a poor outcome (Terzis 1975, Millesi 1981). Other environmental and patient inherent factors can also influence the ultimate success of nerve grafting, including the diameter of the nerve graft (Lux 1986). Free cable grafts have been observed to have central necrosis that is thought to be detrimental to the regeneration of the advancing axons (Lux 1986). One proposed technique for avoiding central necrosis is to place the nerve in a well-vascularized bed (Lux 1986). This technique assumes that the vascularized bed is sufficient to sustain the never graft and ultimately minimal damage would occur. Within the head and neck, most sites are closely related to the large vessels of the neck, but sites of relative low blood flow exist, particularly around the trachea. A different technique to avoid necrosis involves the use of vascularized nerve grafts that contain the surrounding vessels in addition to the neural tissue. These vessels are anastomosed to nearby vasculature which can provide native blood flow to the graft and potetially better performance, as has been demonstrated in the upper extremites (Lux 1986, Terzis 2009). Other grafting techniques, including the use of silastic or polyglycolic acid conduits to help guide grafts, have also been proposed \with some success in treated peripheral nerve injuries (Isaacs 2014). Further loading of these conduits with nerve growth factors, including glial cell-derived neurotrophic factor and neurotrophin-3, has been attempted with demonstrated improved results in nerve regeneration in previous study (Pfister 2007, Moore 2010, Johnson 2009).

The recurrent laryngeal nerve (RLN) is sometimes sacrificed while undergoing thyroidectomy for malignancy. This nerve is responsible for the movement of the ipsilateral glottis, and its loss can be highly detrimental to a patient's ability to voice, swallow and cough. Numerous studies have been done with regard to primary repair of this nerve but occasionally there is a gap in the nerve that requires grafting (Chou 2003). The sacrifice of the nerve is often unplanned, and as such, repair of the nerve will need to be immediate to ensure the lowest amount of morbidity associated its loss. Techniques typically utilized by head and neck surgeons include using free ansa nerve cable grafts or great auricular nerve cable grafts (Li 2013). One group reported the use of free ansa grafts followed by vein wrapping and ultimately showed the there were better results than with conventional reconstruction (Yoo 2012). Further studies have showed that immediate reconstruction of the recurrent laryngeal nerve during surgery using grafts or direct anastomosis showed reasonable voice outcomes (Yumoto 2006). While these methods function to a certain extent, they can certainly be improved upon by evaluating other known methods of nerve repair utilized in other situations. This study searches to evaluate nerve function after repair with multiple methodologies to to assess for an optimal method of RLN reconstruction.

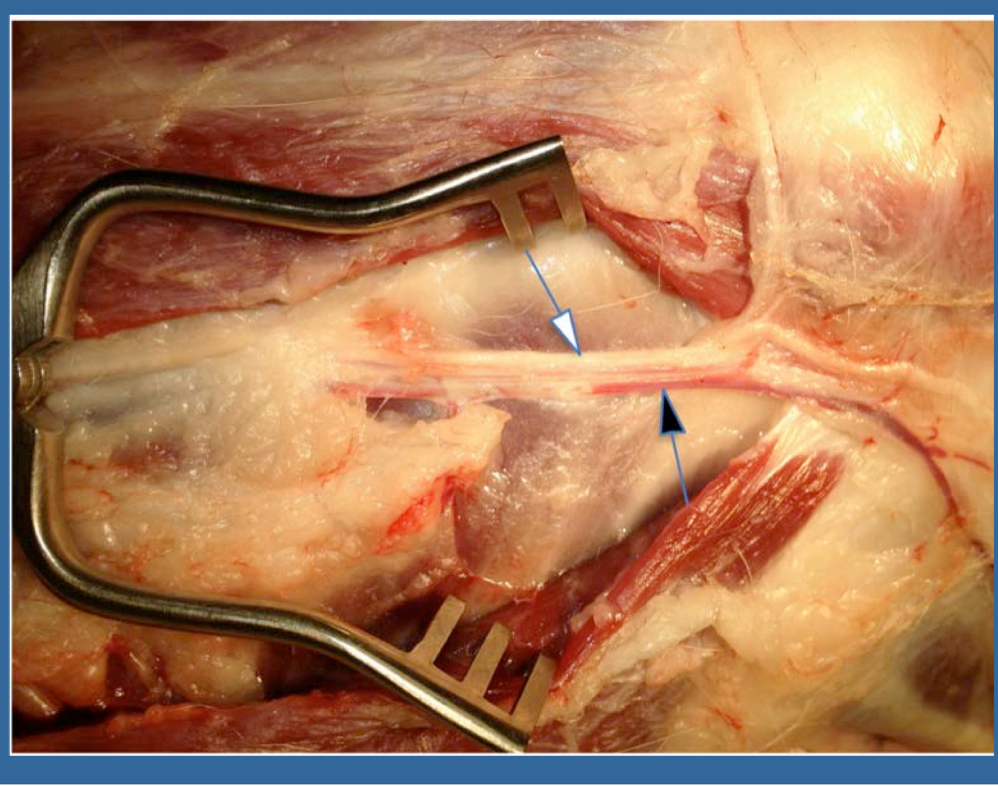

Figure 1: Photo of a dissected canine hindlimb with saphenous nerve (white arrow) and it associated vasculature (black arrow).

METHODS AND MATERIALS

An established canine model of RLN injury was utilized (Paniello 2001). In this model, canine subjects undergo anesthesia per standard protocol and a permanent tracheostomy is placed. RLNs are dissected free and laryngeal adductor pressures (LAPs) are measured with a pressure transducer balloon via electrical stimulation of the nerve. The LAPs are again measured 6 months post-injury as a primary outcome of reconstruction. The recurrent laryngeal nerve is then injured and reconstructed with one of the study methodologies listed in table 1. For the acellular, revascularized and conventional cable grafts, a 5 cm length of RLN was reconstructed. Revascularized nerve grafts were harvested from the saphenous nerve, artery and vein and microvascular anastamosis was performed to the cranial thyroid artery and internal jugular vein. Acellular nerve allografts (5 cm, n=6) were harvested from canine saphenous nerves, engineered via established protocols and implanted into research subjects. The nerve conduits were each 2 cm long and had 0.5 cm of the transected nerve endings loaded into each side, permitting a 1 cm gap. Conventional cable grafts (5 cm, n=6) were also harvested from the saphenous nerve..

Table 1

Methods of Recurrent Laryngeal Nerve Repair (number in experimental group)
Transection with direct neurorrhaphy (n=16)
Reverse autograft (n=8)
Conventional cable graft (n=6)
Revascularized nerve graft (n=4)
Acellular (bioengineered) nerve allograft (n=6)
Silastic conduit with empty carrier (n=4)
Silastic conduit with fibrin-embedded carrier (n=4)
Silastic conduit with fibrin-embedded glial cell-derived neurotrophic factor carrier (n=8)
Silastic conduit with fibrin-embedded neurotrophin-3 carrier (n=8)
Neurotube conduit of woven polyglycolic acid (n=11)

RESULTS

Simple RLN transection with direct neurorrhaphy provided 55.5% (± 12.5%) recovery of baseline LAPs. Reverse autografts provided 60.8% (± 27.5%) recovery of the baseline LAPs. The revascularized grafts and conventional nerve grafts provided a range of recoveries of LAPs. All revascularized nerve grafts were noted to have patent blood supply at canine sacrifice. Two of eleven neurotube reconstructions provided a measurable LAP with an average recovery of 37.1% of baseline. The other 9 neurotube reconstruction did not provide any measureable benefit. Reconstruction with an acellular nerve graft or a neural conduit in any condition provided no measurable LAP recovery.

DISCUSSION

The use of vascularized nerve grafts, acellular nerve grafts, neural conduits or nerve growth facturs in the head and neck or for the RLN has been extremely limited. One group demonstrated that utilizing a free vascularized nerve graft for the facial nerve immediately following sectioning in a select group of high risk patients and demonstrated that muscle movement recovered satisfactorily (Kimata 2005). A further case reported use of a vascularized lateral femoral cutaneous nerve graft to reconstruct the facial nerve (Kashiwa 2010). Another report looked at using neural conduits for canine RLN reconstruction and showed regeneration with a polyglycolic acid tube (Kanemaru 2003).

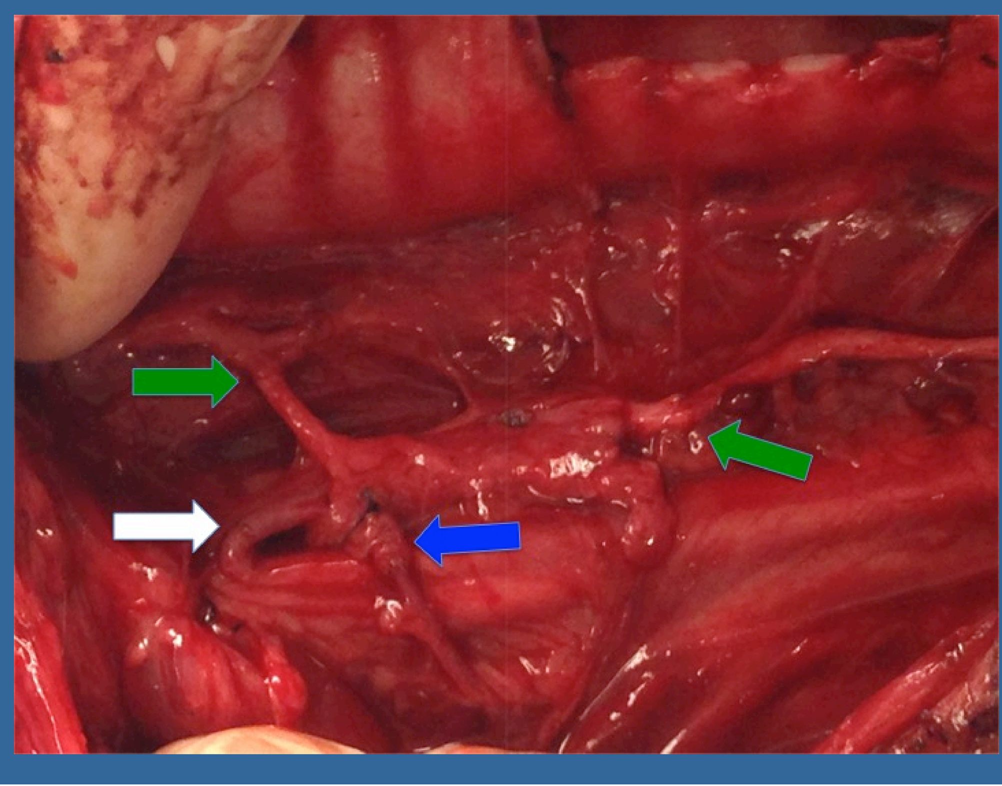

Figure 2: Photo of dissected recurrent laryngeal nerve following removal of 5 cm of nerve and then placement of vascularized saphenous nerve graft showing two nerve anastomoses (green arrows), arterial anastomosis (white arrow) and vein anastomosis (blue arrow).

DISCUSSION (CONT)

The use of acellular nerve grafts and neural conduits has grown in popularity as this technology improves (Isaacs 2014). A number of inherent disadvantages exist to using autologous nerve grafts, including the limited availability of a suitable nerve as well as donor site morbidity such as scarring and numbness. There are FDA approved commercially available acellular grafts and conduits in use for multiple indications today. This is the first study to compare the use of vascularized nerve grafts, acellular nerve grafts and specialized coupling techniques with nerve growth factors for recurrent laryngeal nerve repair. This study has revealed that these specialized methods do not result in additional benefit compared with simple cable grafting or primary repair for reconstruction of the recurrent laryngeal nerve.

CONCLUSIONS

Conventional nerve grafting provided equivalent recovery of laryngeal adductor pressures following recurrent laryngeal nerve repair as to a simple repair or a reverse autograft. Revascularized nerve grafts did not appear to provide additional recovery benefit. The use of bioengineered acellular nerve grafts and nerve conduits for reconstruction resulted in poor recovery of recurrent laryngeal nerve function.

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