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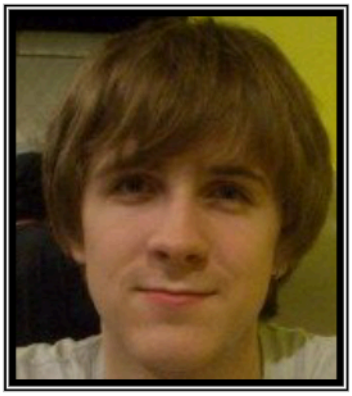
Alternative Methods to Autologous Nerve Grafting for the Regeneration of the Peripheral Nervous System



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INTRODUCTION

The peripheral nervous system is made up of the nerves and neurons that are outside of the central nervous system. These nerves and neurons are used to transport information between the brain and the rest of the body, and when damaged, can severely impact an individual's motor and sensory function [1]. In the United States there are more than 50,000 surgical operations performed each year to repair peripheral nerve damage [2]. When cut, peripheral nerves attempt to grow towards and reconnect to the tissue or muscle they had previously controlled [2].

Neurons are able to effectively regenerate over short distances without any help. However, when the gap they must regenerate across is too wide, a graft is needed to guide the neuron and to prevent the formation of a neuroma [3]. Regeneration is most successful when the severed axons are able to successfully grow through the remnants of the site where the original connection was. In order to help aid in the regrowth of longer gaps a technique called "nerve grafting" is used [4]. Without such grafts, these injuries may never fully heal, and can be permanently debilitating. With the use of these grafts, a much more successful recovery is possible.

Autologous grafts, with their high rate of success, are currently the method most in use today for such situations. However, there are drawbacks to using this method. Autologous grafts require that a nerve be taken from somewhere else on the patient's body. Not only must the patient have an additional operation in order to obtain this nerve, but the patient also must consider a possible loss of function at the location from which this nerve was taken [4].

Because of the drawbacks associated with this method, alternative types of grafts including collagen and non-neural grafts are currently being examined to replace autologous nerve grafting as the primary method of assisted peripheral nerve regeneration. The purpose of this paper is to review the positive and negative aspects of autologous nerve grafting, summarize the capabilities of other forms of grafting to replace the current method, and to present concluding thoughts on the future of peripheral nerve grafting.

AUTOLOGOUS NERVE GRAFTING

The primary method of peripheral nerve grafting in use today is the autologous nerve graft. In this treatment, a comparable nerve is first removed from another part of the patient's body. The nerve is then used to bridge the gap and connect the two ends of the severed nerve, and to then guide the regrowth of the actual nerves [5].

There are several reasons why this method has become so universally accepted. One reason is that by taking the donor nerve from within the patient's body, there is no chance for immunorejection. This is a major benefit of autologous grafting as it nullifies a significant portion of the risks associated with implanting a foreign material into a patient's body. The autologous graft also has a fairly high success rate, and usually restores the majority of functionality to the damaged location. This graft also provides a support structure that promotes regeneration [6].

However, the use of the autologous graft as a nerve grafting method is not perfect, and there are several disadvantages. The most prominent disadvantage to this method is the possibility of a loss of function at the site where the donor nerve was taken. By removing a nerve from a fully functioning part of the body, there is the risk that full functionality at this location will be lost. In addition, the patient may have complications from the additional surgery, and is subjected to an increased risk of infection at the donor site. This method also can lead to incomplete regeneration of the damaged nerve, even with the use of the autologous graft [2].

Another detriment to autologous grafts is that there are a limited number of locations that can be used as a donor site, as the selected nerve must have a similar structure to the nerve that was removed. In addition, another negative outcome is the possibility of the death of the donor tissue because of an unsuccessful attempt to attach it to the damaged location [5]. With this complication, the patient would be left with two damaged locations and no restoration of function in the original location.

NON-AUTOLOGOUS NERVE GRAFTING

Attempts have been made to discover a method to assist in peripheral nerve regeneration without involving tissue removed from another location on the patient's body. To eliminate this requirement, graft methods have been created that involve the use of extracellular matrix (ECM) of non-autologous tissue instead of autologous tissue [4]. However, there are disadvantages with the use of nonautologous tissue. The cells native to the non-autologous tissue must be completely eliminated in order to remove the risk of immunorejection, and this is difficult to do without the destruction of the ECM [6]. If the tissue is to be used as a nerve graft, it is vital that

the ECM remain intact.

The extracellular matrix, or ECM, plays an important role in nerve regeneration. The ECM is the material that surrounds cells, and molecules within the matrix can help guide, promote, or inhibit the growth of neurons. It may be necessary to emulate the ECM in order to accurately guide the axonal regeneration. Attempts have been made to create a non-neural graft that satisfies all of the criteria above. However, it has been difficult to create a graft that maintains the structure of the ECM while eliminating cellular debris because of limitations when using thermal, radiation, and chemical treatments, and because of this, bioartificial grafts have had lower success rates than autologous grafts [1].

There are a variety of techniques used to create a graft using non-autologous tissue. These techniques include thermal, radiation, and chemical treatments, but thermal is the most common method in use today [6]. When tissue is subjected to thermal treatment, it goes through a series of freeze-thaw cycles. These cycles kill the cells in order to make the graft acellular, but they damage the native ECM and do not extract the cellular debris from the tissue [2]. After this graft is implanted into the patient, the cellular debris left behind must then be cleared out by the patient's immune system before regeneration is able to begin [6]. Radiation treatment does not destroy the extracellular matrix to the same extent, but it also fails at extracting the cellular debris from the material. Because of the presence of drawbacks in both of these creation techniques, it is difficult to create a graft that successfully removes cellular debris while leaving the ECM intact.

Chemical treatment is able to effectively wash away the cellular debris, but it also causes significant damage to the ECM. However, recent advances have created chemical treatments which are able to effectively wash out cellular debris while still leaving the ECM largely intact [6]. Because of these advances, chemical treatment may be able to one day replace thermal treatment as the primary method of decellularization and be much more successful at leaving the extracellular matrix intact.

NON-NEURAL NERVE GRAFTING

The first type of non-autologous graft that will be discussed is the non-neural, or bioartificial, nerve graft. The use of this graft attempts to avoid the disadvantages presented by the autologous graft, while still promoting peripheral nerve regeneration. In order to achieve this result, the graft must be made out of a material that has similar characteristics to that of the nerve it is guiding. In addition, the graft must also be biocompatible and biodegradable in order for the graft to be considered a fully acceptable placement [3].

Bioartificial grafts use nonautologous tissues and make use of the presence of both Schwann cells, which guide the neuron regrowth, and extracellular matrix. These grafts must both bridge the gap caused by the patient's injury and help promote the regrowth of neurons across this gap. The extracellular matrix of the nonautologous tissue may be the main component of the graft used to improve the regrowth of neurons [7].

One method of increasing the effectiveness of an artificial material as a functioning nerve graft is to seed it with Schwann cells. Schwann cells are myelin producing cells required for axonal regeneration by guiding the axons and producing adhesion molecules [6]. Without the use of Schwann cells it is much more difficult for neurons to regenerate across long gaps. In

the most effective experiments that involve collagen as the nerve graft, Schwann cells were seeded within the collagen in order to promote growth [5].

COLLAGEN NERVE GRAFTING

Another alternative to the autologous nerve graft that is being developed is the use of a collagen mold to create a graft between the two severed ends of a nerve. Collagen is one of the major components that make up the extracellular matrix. This material has had a large degree of success in other types of surgical procedures, and has also been used in nerve repair [4]. It is a viable material for use as a graft as it provides a high level of permeability when placed within the body, is biodegradable, and allows different cell types to grow within it [4].

What makes collagen even more useful as a nerve graft is that it can be shaped in structures that are able to promote nerve regeneration [4]. Collagen itself actually plays an important role in nerve regeneration, and it is possible to control the porosity of collagen structures. This control makes it possible to decide the environment in which the nerve regeneration takes place [5].

COMPARISON OF METHODS

At this point in time, the autologous nerve graft has had the highest success of nerve regeneration. The complications involved with an autologous graft make it desirable to find a method that could replace it. Results from experiments conducted by scholars such as Felix Stang, Hisham Fansa, Gerald Wolf, and Gerburg Keilhoff indicate that collagen does not appear to be an acceptable material to use as a nerve graft [4]. In their 2005 experiment, the authors were able to obtain slightly better regeneration rates by adding Schwann cells to the collagen grafts than they were by using the collagen grafts alone. Even when using the Schwann cells, however, the regeneration capabilities of neurons within a collagen graft is much lower than if an autologous graft had been used. This finding leads to the conclusion that while collagen grafts may not be an adequate replacement to autologous grafts, the presence of Schwann cells appears to be able to improve the regeneration rate of neurons in non-neural grafts, and another type of graft may therefore be enhanced with such cells.

In contrast, another experiment conducted in 2003 by Yueh-Sheng, Chien-Ju Liu, Chun-Yuan Cheng, and Chun-Hsu Yao entitled "Effect of bilobalide on peripheral nerve regeneration" resulted in a very different outcome when using collagen as a nerve graft. In this experiment, the researchers attempted to combine collagen with laminin, a neural growth stimulant, and fibronectin, a water-binding protein to create their graft. They then attempted to combine this graft with bilobalide, an extraction taken from *Ginkgo biloba* leaves. They found that this mixture significantly promotes peripheral nerve regeneration, but that it is crucial to use the correct dosage of bilobalide, as a large dosage can actually inhibit growth, and a dosage that is too small would not be effective [8].

Non-neural grafts appear to have potential as a replacement method to autologous grafts in the near future. With the development of improved methods for preparing nonautologous tissue along with other improvements associated with additional experimentations, non-neural grafts may be able to reach the same level of

success or perhaps even surpass this more traditional form of grafting. Because non-neural grafts do not seem to have the disadvantages that are associated with the autologous graft, they could easily become the method of choice for peripheral nerve regeneration, once equivalent success rates are achieved.

SUMMARY AND CONCLUSION

As of this point in time, autologous grafts are the most widely used form of nerve grafting. These grafts have a higher success rate compared to other grafting methods being developed, but drawbacks associated with this graft type make it desirable to develop alternatives. Experiments involving collagen as the base for a nerve graft have shown that this method is probably an ineffective form of treatment for the regeneration of peripheral nerve cells. However, these studies have also shown that there are benefits to imbedding Schwann cells into implanted grafts.

It has become hard to make any further advances with collagen as the base for nerve grafts, as it is difficult to remove the drawbacks inherent in using collagen as the base for the graft. The collagen tubes' wall thickness, porosity, diameter, and alignment of the inner skeleton must all be manipulated in order to produce a good alternative for nerve grafting [4].

Even with the manipulation of these factors, animal studies that made use of collagen grafts for nerve repair showed a permanent loss of motor function and impaired sensitivity. In general, very few myelinated fibers are able to regenerate through a collagen conduit and enter the distal nerve segment, even when Schwann cells are seeded in the graft to increase the regeneration abilities [4]. Importantly, collagen grafts that made use of Schwann cells did have an increased regeneration rate, but this rate is not achieved to the point that it is comparable to the regeneration rate of autologous grafts. In the experiment involving bilobalide, it appears to be difficult to correctly manipulate the bilobalide dosage in order to effectively create a nerve graft that would ever surpass the success rate of the autologous graft. Differences in suture size and extent of the damage would make it difficult to judge the correct dosage of bilobalide, and the results would end up being less predictable than the current method.

In contrast, non-neural grafts appear to have a significant chance at becoming the dominant grafting technique. Recent advances in development techniques involving the treatment of tissues with chemicals for non -neural grafts have been developed that leave the native ECM intact while removing cellular debris [6]. If this new technique is refined even further, it may be used to create a material that is viable for use as a nerve graft. It may then be possible to increase the success rate of the graft by seeding the inside of it with Schwann cells. This combination may be able to lead to a grafting device that has a similar success rate to that of autologous grafting but without the drawbacks associated with an autologous graft.

The benefits to using tissue not taken from the patient's body remove the complications associated with the autologous graft, including the additional surgery, the limited availability of donor nerves, and the possibility of a loss of function at the donor site. Various advantages and disadvantages associated with each of the methods described in this paper are summarized in Table 1.

As can be seen in Table 1, when the advantages and disadvantages of autologous and non-neural grafts

are directly compared, as shown, it is evident that if non-neural nerve grafts are able to obtain a success rate comparable to that of the autologous nerve graft, it could easily replace autologous as the most used method for peripheral nerve regeneration.

It is clear that while the autologous nerve graft is the most popular method in use today because of its high rate of neural regeneration, there are still enough drawbacks that make it desirable to find an alternative. The most promising alternative at this time appears to be the non-neural graft. This type of graft has the potential of a high success rate with none of the drawbacks currently associated with the autologous graft.

Method	Advantages	Disadvantages
Autologous	High success rate, no chance for rejection	Additional surgery, possible loss of function at donor site, chance for infection at donor site, limited donor site locations
Non-neural	Only one operation, low to no chance for rejection, few complications	Currently not as high success rate as autologous, must treat to make acellular
Collagen	No chance of rejection, easily obtained materials	Low or unpredictable success rate

Table 1: A Comparison of Grafting Methods for Peripheral Nerve Regeneration

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