HISTOLOGIC COMPARISON OF CHRONIC IMPLANTATION OF NERVE CUFF AND EPINEURAL ELECTRODES

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ABSTRACT

The effect of chronic implantation of two types of nerve cuff electrodes (epineural and cuff) was investigated in the sciatic nerves of 16 rabbits. There were ten epineural, ten cuff, five sham cuff, five sham epineural, and two unoperated sciatic nerves used as controls.

Three representative cross-sections of each nerve at levels proximal to, distal to, and at the level of the electrode were analyzed histologically. Sections were analyzed using hematoxylin-eosin, bodian, luxol fast blue, and Masson trichrome stains. Evaluation included quantitative and qualitative assessment of any perineural tissue reaction in addition to specific changes including demyelinization, fatty degeneration, inflammation, granuloma formation, and giant cell reaction. Particular attention was directed to alterations in the epineurium and epineural vasculature about the circumference of the nerve. Quantitative measurements were performed by a point-count method using a morphometric grid.

When comparing the implanted groups (epineural and cuff) to the sham implanted, and the control group, there was no statistically significant difference found in the amount of epineural or perineural scar tissue (fibrous tissue reaction). There was also no significant increase found in the thickness of the epineurium in the region of the epineural electrode when compared to the sham and control groups. Special staining techniques did not demonstrate any evidence of axonal damage in either group.

INTRODUCTION

Chronic implantation of nerve electrodes was first performed by Liess in 1932 (16). This technique gained rapid acceptance and has been used both for recording nerve impulses and electrical stimulation (6-9,19,21,24). Mechanical irritation and injury of nervous tissue and its blood supply resulting from attachment of the electrode has been a point of concern (11). As early as 1956, electrodes were specifically designed to minimize the potential for neural injury (4,5,11).

The cuff electrode, circumferentially wrapped around the nerve, provides a convenient and secure method of attaching the electrode to the nerve. Cuff electrodes have been used for a number of clinical applications including diaphragm pacing (9), correction of footdrop (24) and pain control (15). They have been used extensively in chronic animal studies for stimulation (3,10,11,23).

Mechanical failures of cuff electrodes are rare. In a recent review of 93 patients following implantation of the peroneal nerve to correct footdrop in hemiplegic subjects (25) or phrenic nerves for diaphragm pacing (6), only one electrode/lead failure was reported (25). Glenn believed the absence of a progressive rise in the threshold to stimulation and minimal histologic changes in the phrenic nerves examined after 1 or 2 years supported the conclusion that no major damage to the nerve occurred due to the electrode and prolonged electrical stimulation (8). Other studies in which the cuff electrode was used to pace the diaphragm via stimulation of the phrenic nerve demonstrated functioning electrodes in 15 patients after 10-16 years (8). Waters reported seven electrodes used to stimulate the peroneal nerve were still functioning 10-12 years after implantation (25). Nevertheless, the potential problem of epineural fibrosis associated with a circumferential cuff electrode remains a concern since for many applications in functional electrical stimulation the projected life span of the patient is 40 years or longer after implantation.

An alternative to the cuff electrode is sutured directly to the epineurium (the connective tissue covering peripheral nerves) on the side of the nerve. Nashold (21) implanted epineural electrodes in 13 patients for control of chronic pain in 1977. No nerve damage was reported, but histologic analysis was not performed (20). Nashold believed the epineural electrode to be superior to the cuff electrode because the design reduced the required surgical dissection, eliminated the constriction of a cuff, and potentially, circumferential perineural fibrosis.

The present study was performed to critically compare the relative safety and tissue effects, via histologic analysis, of the passive implantation of two types of electrodes: the nerve cuff electrode and the epineural electrode.

MATERIALS AND METHODS

CUFF ELECTRODES: The cuff electrodes consisted of a 1 mm diameter platinum-plated titanium button, spot-welded to 25 strand stainless steel teflon insulated lead wire. The titanium button was attached by medical grade adhesive to 7 mil medical grade silastic sheeting reinforced with dacron mesh (Dow Corning). The width of the cuff encircling the nerve was 3 mm.

EPINEURAL ELECTRODE: The epineural electrodes consisted of the same 1 mm diameter, platinum-plated titanium button, spot-welded to 25 strand stainless steel teflon insulated lead wire used for the cuff electrode. The button is mounted on a 5 mm diameter, circular-shaped piece of the same 7 mil medical grade silastic sheeting used for the cuff electrodes. The electrodes were implanted for an average of 127 days with a range of 112 days to 155 days.

SHAM PROCEDURE: In a sham procedure the electrode was implanted and then immediately removed. Shams were utilized in the investigation to determine the iatrogenic mechanical effects of operative electrode placement. This allowed us to examine the effects of acute trauma resulting from surgical dissection and implantation versus secondary changes resulting from chronic electrodes implantation.

RABBITS: Sixteen adult male New Zealand White rabbits were used for this study. The average weight of each rabbit was 4.47 Kg with a range of 4.20 Kg to 4.80 Kg. The sciatic nerve of the hind limb was selected for implantation.

All rabbits underwent electrode implantation on at least one limb and two rabbits had the sciatic nerve of the right hind limb used strictly as a control. Ten epineural electrodes were implanted, four on the left sciatic nerve and six on the right. Ten cuff electrodes were implanted, six on the left sciatic nerve and four on the right. Five sham epineural procedures were done, four on the left sciatic nerve and one on the right. Five sham cuff procedures were done, two on the left sciatic nerve and three on the right.

SURGICAL PROCEDURE: All rabbits were given an injection consisting of a mixture of Rompun-50mg/Kg, Acepromazine-1mg/Kg and Ketamine-35mg/Kg. Anesthesia was maintained with Rompun-20mg IM every 1 to 1-1/2 hours as needed. With the rabbit in the prone position, the sciatic vein is identified on the lateral surface of the thigh. The first portion of the biceps femoris is freed from the superficial head of the semimembranous enabling separation of the two portions of the biceps. The first head of the biceps is elevated and the muscle bluntly divided exposing the branches of the sciatic nerve which lie beneath it. The cuff or epineural electrodes were attached to the sciatic nerve using microsurgical instruments and 3.5 power magnification. All electrode implantation procedures were performed by the same surgeon trained in microsurgical technique.

ELECTRODE ATTACHMENT TECHNIQUE: Attachment of epineural electrodes to the epineurium is relatively atraumatic and simple to perform (18). Repair of nerves by epineural sutures represents the standard method of nerve repair. It is readily adaptable to electrode attachment. A #9 nonabsorbable suture is used to attach each corner of the epineural electrode to the side of the nerve. The cuff electrode attachment technique involves obtaining circumferential nerve exposure and wrapping the electrode sleeve around the nerve. The overlapped portion of the cuff is sutured to the underlying portion of the cuff using a #9 nonabsorbable suture.

EUTHANASIA: At the time of implant removal, the rabbits were sedated by using the same anesthetic mixture as was used for electrode implantation. On the average, electrodes were explanted four months after implantation. Using the previous incision as a guide, the sciatic vein was exposed and cannulated to permit a 100 ml saline pre-wash. The rabbits were then given an intravenous overdose of phenobarbital followed by a second wash with a saline solution.

PATHOLOGY: The electrodes were removed from the nerve and the resected nerve segments were fixed in 10% formalin. The electrodes were removed prior to nerve sectioning and the type of electrode noted. Three representative cross-sections of each nerve proximal to the electrode, at the level of the electrode, and distal to the electrode, were submitted for paraffin embedding. The sections were analyzed by hematoxylin-eosin, bodian, luxol fast blue and Masson trichrome stains.

Histologic examination included qualitative and quantitative assessment of the perineural fibrous reaction in addition to assessment of other specific changes including demyelination, fatty degeneration, inflammation, granuloma formation and giant cell reaction. Two pathologists (SR and GK) analyzed the slides in a blinded study design and were not informed regarding the type of electrode, cuff or epineural, which had been placed on the nerve. They were also unaware of whether the cross-section of the nerve undergoing examination was obtained proximal to, at, or distal to the level of the electrode.

Slides were labeled in all four quadrants by a neural histology technician who recorded the level of the nerve specimen relative to the electrode and also the slide quadrant which contains the electrode button contact site.

The pathologist examined the entire nerve and noted specific areas of increased fibrosis, demyelination and fatty degeneration by quadrant as well as noting normal architecture. Particular attention was directed to alterations in the epineurium and epineural vasculature about the circumference of the nerve. In this way a detailed map of the histology of each section was made and later compared with the type and location of the electrode. Quantitative measurement of tissue reaction (fibrosis) was performed by a point-count method using a morphometric grid (17,26). The final score consists of the ratio of the total points of fibrosis to the number of nerves and levels of paraffin block examined (total points/number of nerves examined multiplied by the levels). The statistical significance ($p<0.05$) of the difference between the final scores of cuff versus epineural electrode was determined by statistical analysis (Chi-square method).

RESULTS

The effect of chronic implantation of epineural electrodes on the sciatic nerves of rabbits was evaluated histologically using a point-counting technique and four quadrant analysis. In addition to standard hematoxylin and eosin stain, special stains (see Materials and Methods) were used to look for any evidence of axonal damage as a result of implantation.

When comparing the implanted groups (epineural and cuff) to the sham implanted, and the control group, there was no statistically significant difference found in the amount of epineural or perineural scar tissue (fibrous tissue reaction). There was also no significant increase found in the thickness of the epineurium in the region of the epineural electrode when compared to the sham and control groups. Special staining techniques did not demonstrate any evidence of axonal damage in either group.

The analysis of the results of chronic implantation of cuff and epineural electrodes without leads would seem to indicate no significant detrimental effects of either type of electrode. These results should be analyzed however, with the understanding that no lead wire was attached to the electrode. It may be that when the electrode is connected to the lead wire combination that significantly different results from these will be found, and this is the next area which will be investigated.

DISCUSSION

Implantable nerve electrodes have many advantages in functional electrical stimulation (FES) due to their stability, reliability and low energy requirements. Although nerve cuff electrodes have been used for a variety of clinical applications (6,8,9,15,19,21,24), it has been demonstrated that they can cause nerve injuries (8,9,14,24). This injury is thought to arise most often due to the technique of implantation of the electrode. In comparison to the cuff electrode, placement of an epineural electrode requires much less surgical dissection and nerve manipulation for implantation since it is not necessary to dissect completely around the nerve. Also, the risk of post-operative circumferential epineural fibrosis and secondary constriction by scar tissue is avoided since the electrode only contacts one side of the nerve.

Complications have been reported, however, including nerve injuries and late infection. Experience has indicated that the source of nerve injury associated with implanted electrodes is probably due to the physical contact of the electrode and not the result of the electrical stimulation current which is usually below 20 ma (6,12,24). Kim, in a study of phrenic nerves obtained at autopsy from seven patients with chronic ventilatory insufficiency, states that "the fact that the nerves from two patients, each stimulated for about two years, showed no histologic changes suggests that injury to the nerves was not caused by electrical stimuli but rather was secondary to the technique of application and fixation of the cuff electrode to the nerve" (13).

The application of cuff electrodes requires dissection completely around the nerve since by design they encircle the nerve. The fibrotic capsule which forms on the epineurium underneath the circumferential cuff electrode is analogous to the circumferential epineural fibrosis which occurs in peripheral compressive neuropathies such as carpal tunnel syndrome. Nielson has reported compression of a nerve trunk due to the wrapping of the cuff electrode around the peripheral nerve (22). Glenn believed the cuff-type electrode and its method of implantation were responsible for the injury to the nerves at surgery and that long-term success of diaphragm pacing is threatened mainly by damage from the nerve cuff electrode (6).

Besides the mechanical trauma of cuff implantation and circumferential epineural fibrosis, secondary nerve swelling within the cuff can also cause constriction (2). In a study of 31 implanted electrode units, McNeal and Waters reported two cases of nerve palsy (19). Both occurred within one day of surgery and were thought to be due to an excessive tissue reaction to silastic or to surgical handling which caused the nerve to swell and become constricted within the cuff electrode. Both patients subsequently recovered and the electrodes functioned effectively following surgical exploration and placement of a larger cuff electrode. Late infection apparently precipitated by seroma formation about the implant, often accompanied by inflammation and pain, was observed in approximately 20% of the footdrop cases performed at Rancho Los Amigos Medical Center (19,25). Infection was also observed in five of 37 respiratory patients (8).

Agnew devised a spiral cuff-type electrode which he implanted around 16 common peroneal nerves in adult cats (1). "Chronic" type neural damage, specifically axonal loss with connective tissue replacement, was observed in close association with, and remote from, the electrode implants. Although the primary pattern of neural damage observed strongly suggested a compression-type insult to the peroneal nerves in his series, the actual mechanisms were unclear (2).

To avoid the complication of nerve cuff electrodes, Nashold began using an electrode that was sutured to the nerve epineurium, thus reducing the dissection required and eliminating the constriction of the cuff (21). This electrode (called an epineural electrode) consisted of a platinum-iridium button (2x1 mm) mounted on a sheet of dacron impregnated with silastic. Nashold believes the epineural electrodes are superior to cuff electrodes and that their use improves the success rate of peripheral nerve stimulation. He implanted epineural electrodes in 13 patients on the median, ulnar and sciatic nerves for control of chronic pain in 1976/77. No complications or damage to peripheral nerves were reported, but histology was not performed (20).

This study, which critically analyzed the perineural tissue reaction to both the epineural and cuff type electrodes, did not show any statistically significant differences between the two types of electrodes. In addition, during the period of chronic implantation (four months average), there was no evidence of internal damage to the nerve such as internal thickening or loss or change in axon configuration compared to the control groups. It must be remembered, however, that in this study the electrodes were implanted without their lead wires attached. It is possible that when the next phase of this study evaluating the effects of chronic implantation of cuff and epineural electrodes with their lead wires attached is accomplished that quite different results may be found.

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