Neurolysis and upper trunk brachial plexus birth palsy

To The Editor: We read the article by Andrisevic et al.1 with interest (Andrisevic E, Taniguchi M, Partington MD, et al: Neurolysis alone as the treatment for neuroma-in-continuity with more than 50% conduction in infants with upper trunk brachial plexus birth palsy. Clinical article. J Neurosurg Pediatr 13:229–237, February 2014). The authors are to be commended for their efforts to improve treatment of patients with this severe birth trauma that has lifelong implications; however, we do have some concerns about the applied treatment and analysis.

The authors evaluated 441 infants, of whom 44 (10%) underwent nerve surgery: nerve grafting in 14 and neurolysis of the upper trunk in 30. Of the 30 patients who underwent neurolysis, 13 did not meet the inclusion criteria. As a result, 17 (39%) of the 44 surgically treated patients were included in the present analysis. Compound motor action potential (CMAP) responses were recorded after direct electrical stimulation was applied proximal and distal to the superior trunk neurona. The authors used the Laurent and Lee treatment algorithm,6 which employs a 50% conduction threshold as the cutoff for neurolysis alone versus neurona resection. All patients included in the study had a neuroma-in-continuity with more than 50% conduction across the neuroma, and subsequently C-5 and C-6 neurolysis was performed. Based on their results the authors concluded that their group of patients benefitted clinically from the neurolysis. We would like to address a number of issues concerning the analysis and conclusions that need attention.

Surgical Method in Relation to the Pathophysiology

The most important issue is the authors’ claim that neurolysis had a therapeutic benefit in their series. Neurolysis, as they performed it, was described as “making multiple longitudinal incisions into the thickened epineurium of the neuroma, until axonal tissue could be visualized.” The authors did not include a control group consisting of similar patients in whom they did not make multiple longitudinal incisions. Instead, they made a comparison with cases reported on in the literature. We are not aware of any study supporting the claim that this type of surgical intervention indeed improves axonal regeneration and, consequently, has a beneficial effect on nerve function recovery. In our opinion, the authors’ claim does not hold up in view of the pathophysiological process underlying brachial plexus birth palsy (BPBP). In severe traction lesions of the brachial plexus with axonal rupture, loss of basal lamina tube continuity, fascicular rupture and fibrosis typically result in a neuroma-in-continuity. Neurological recovery is limited because axons cannot successfully cross the lesion site due to an increase in extracellular matrix and expression of growth-inhibiting proteins such as semaphorin 3A by epineural and perineural fibroblasts.13 Additionally, functional recovery is impaired due to axonal misrouting.7 How neurolysis could improve axonal recovery in such a complex setting is difficult to understand, unless the selected patients had a predominantly axonotmetic lesion.

To support their view, the authors wrote, “Neurolysis is believed to reduce high intraneuronal pressure, improve blood flow, and alleviate the physical barriers to regeneration.”8 The report by Nelson to which they are here referring, however, does not contain any original, experimental, or clinical work showing that these factors play a role in BPBP or are the cause of frustrated regeneration, nor that neurolysis has a beneficial effect on regeneration.

We agree with the authors that absent neurological recovery in a child with BPBP is an indication for surgical exploration. When the brachial plexus elements show fascicular continuity across the lesion site and when the muscles respond to direct electrical stimulation with clear contractions, the surgery is ended. We label this procedure as “neurolysis”—that is, a diagnostic procedure. The recovery that subsequently takes place is the logical result of completing axonal outgrowth through the damaged area, to which neurolysis did not contribute.

Intraoperative Neurophysiology

The authors stated that the protocol they followed at their institution most closely mirrors that of Laurent and Lee.6 It is, in this respect, crucial to stress that the applied methodology has never been validated, and the cutoff point of 50% conduction across the neuroma was arbitrarily set in the original paper. In our opinion, the authors should have highlighted and discussed this more prominently. The authors did not discuss the potential implications of the fact that the infants in their series were twice as old as those in the Laurent and Lee series. The mean age of patients in the Laurent and Lee series was 5 months (range 2–18 months) whereas that in their own series was 10 months (range 6–19 months). The presence of 50% conduction across a neuroma-in-continuity at 5 months cannot be compared to similar findings at 10 months.

The authors’ choice for the applied electrophysiological method is not clear. The underlying pathophysiological mechanisms were thoroughly investigated with alternative
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intraoperative testing. Nerve action potential recording, for instance, requires regrowth of axons across the lesion site, which is indicative of commencing successful reinnervation. Comparing the amplitude of CMAPs across a lesion site, however, is usually done to diagnose conduc-
tion blocks or demyelination in neuropathies (for instance, compres-sion at the carpal tunnel or elbow). The authors’ choice to compare CMAPs proximal and distal to a nerve traction lesion should be clarified in more detail because it is an unusual method by which to measure axonal loss.

Unfortunately, not all relevant publications on intra-
operative neurophysiology were referenced in the article. The available literature contains relevant data that put the authors’ conclusions in a different perspective. König et al. were very unsatisfied with the outcome in their 5 patients after performing neurolysis “only,” when conduction over the neuroma was demonstrated. We have studied the predictive value of nerve action potentials and CMAPs in 95 BPBP patients. Although axonotme-
sis, neurotmesis, and avulsion could be distinguished on group level, we were unable to identify valid cutoff points for the individual patient to facilitate the decision of whether to cut a neuroma-in-continuity and graft or leave the nerve-in-continuity. We therefore do not share the authors’ opinion that intraoperative electrophysiological testing is of paramount importance to surgical decision making during primary exploration.

Chin et al. used CMAP recordings after direct intra-
operative stimulation, as Andrisevic et al. did, but instead of comparing the amplitude resulting from stimulation proximal and distal to the neuroma, they looked at the morphology of the CMAP to help in the decision-making process. Roughly two-thirds of their surgically treated patients (22 of 32) underwent neurolysis only, which resulted in good recovery of abduction and elbow flexion but poor recovery of external rotation.

Functional Recovery and Interpretation

The authors qualified the results of shoulder function and of elbow flexion recovery as good, while functional external rotation recovery occurred in only one-third of their patients. In our opinion, external rotation is the hallmark function of recovery in BPBP patients. We are well aware that the results from nerve grafting or nerve transfer are not spectacularly better as compared to the authors’ results. Improving the outcome of external rotation is one of the most important targets to achieve in treating these children. In that respect, the authors’ treatment paradigm unfortunately did not add to improving external rotation. In fact, biceps function recovery is not the only goal of nerve reconstruction. Biceps function is employed by most authors as a proxy to diagnose the severity of the upper trunk lesion and is thus used as an indicator of nerve reconstruction to improve elbow flexion and shoulder function, including external rotation.

Analysis and Reached Conclusion

The authors claimed to have demonstrated the superi-ority of neurolysis in the treatment of BPBP over conser-vative treatment. This claim was based on a selection of 17 patients from a total group of 30 treated with neurolysis. This might have created an inclusion bias. Outcomes in these patients were then compared to those in 7 conservatively treated patients reported on in literature by means of a numerical conversion. This conservatively treated patient group from the literature was already biased by inclusion, as 27 of 66 patients were not included in the analysis in the original paper.

The authors discarded the results from Toronto Sick Kids group (led by Clarke, in the article by Lin and col-
leagues’), which led them to conclude that neurolysis alone must not be used for treatment of BPBP. The main reason for this condemnation is the limited number of patients in Lin and colleagues’ neurolysis group (n = 8), which serves in fact as a control group for grafting (n = 48). This number is small indeed but is similar in size as the group that Andrisevic et al. extracted from the literature and used as their control group (n = 7) for neurolysis (n = 17).

It is, all in all, in our opinion questionable whether the methodology followed by the authors can really support their conclusion, which promotes neurolysis as surgical treatment in BPBP infants.

We would like to conclude with the following quote from Sunderland:

“When neurolysis performed under these conditions is followed by recovery it is only natural to attribute the improvement to the surgical procedure which, it is assumed, has removed a barrier to regeneration. The value of neurolysis in these cases is, however, difficult to assess…. It is, therefore, impossible to exclude the possibility that neurolysis in these cases is merely coincidental to delayed, but normal, regenerative processes that would, in any event, have resulted in recovery.”

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Disclosure

The authors report no conflict of interest.

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RESPONSE: We thank Drs. Pondaaag and Malessy for the thoughtful analysis of our article.

As Sunderland pointed out in his original article, classification of nerve injuries helps us define the spectrum of nerve injuries to determine prognosis and treatment. Accurate description of the extent of nerve injury helps us determine the extent of treatment necessary to manage that injury. On the least severe end of the Sunderland scale, with the neuropraxia injury, all experts would agree that it is mild enough that the natural history will bring about a full and complete recovery without surgical intervention. On the most severe end of the Sunderland scale, with the neurotmesis injury, all experts would agree that it is severe and the best outcome comes from surgical treatment with excision of the area of nerve injury and nerve grafting. What we are proposing is that there are nerve injuries that exist that are severe enough that they will improve after surgical decompression and external neurolysis, but not so severe as to require excision and nerve grafting.

On the less severe end of nerve injury, our attempt is to identify those children who will not fully recover without surgical intervention. In this regard, we have used the information available from a well-designed natural history study to select children greater than 6 months of age, as 39 of the 66 children in his study showed return of biceps function between 3 and 6 months of age. Ten percent of the children seen in our Birth Brachial Plexus Clinic underwent surgery (44 children treated surgically of 441 children evaluated). Although we ethically cannot randomize children who we think would benefit from surgery, we believe our surgical cohort clearly represents children who would not have gotten better without an operation.

On the more severe end of nerve injury, we treated 44 children surgically. Eleven of these children had the most severe injury, neurotmesis, with less than 50% conduction across the nerve injury, and were treated with the standard nerve resection and grafting.

As a group of combined specialists, with Dr. Partington (pediatric neurosurgery), Dr. Van Heest (orthopedic hand surgeon), and Dr. Taniguchi (pediatric rehabilitation), we strive to combine knowledge of clinical assessment, intraoperative nerve injury anatomy, and intraoperative neurophysiology to improve the accuracy of the evaluation of the neural lesion in neuroma-in-continuity and thereby help in surgical decision making. As Sunderland outlined, not all axonotmesis injuries are equal, and they do not all need to be surgically excised and grafted. Although the criteria of Laurent and Lee are historical, these data are the best presently available, to our knowledge, to help delineate the extent of axonotmesis injury. With use of these criteria and a treatment (neurolysis alone) that preserves the nerve function that was present prior to surgery, we are reporting that at a follow-up of greater than 2 years, 14 of 16 children had useful hand-to-mouth function (Active Movement Scale [AMS] score of 6–7), 11 children had useful shoulder abduction and shoulder flexion (AMS score of 6–7), and 5 of 15 children had useful shoulder external rotation (AMS score of 6–7). Thus, there are children with axonotmesis injuries who can be successfully treated with neurolysis alone. At our treatment center, the hallmark of success of primary nerve surgery is return of elbow flexion and shoulder abduction/flexion, as shoulder external rotation can be successfully treated with tendon transfer.

Responses to the other points of the Letter to the Editor are outlined below.

Surgical Method in Relation to Pathophysiology

As pointed out by Drs. Pondaaag and Malessy, the exact mechanism by which external neurolysis of a conducting neuroma influences recovery remains incompletely understood. The observation that we did not include a control group of patients in whom the involved nerves were exposed, but not incised, is accurate. This group would be similar to what they describe as “neurolysis” in their series—that is, the plexus is exposed, dissected free of surrounding tissues, and then subjected to electrophysiological testing only. Nevertheless, since it is our experience that the addition of simple external neurolysis has not resulted in significant injury (as identified in the postoperative AMS assessment), we feel that this is a reasonable extension of the procedure Drs. Pondaaag and Malessy describe. It is understood and recognized that much of the benefit of this operation is likely achieved by the simple, but sometimes tedious, task of dissecting the plexus free of the surrounding muscles and other tissues. Indeed, it is often the case (in our hands) that the external neurolysis of neural structures is accomplished.
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when one is dissecting off attached muscle and other tissue. The results in our series do demonstrate a significant change in AMS scores, when patients were at an age at which spontaneous recovery is less likely. To prove causation, however, is not within the scope of this paper, but we do feel that we have provided evidence in support of this association.

It is safe to say that not every injured peripheral nerve needs to be resected and grafted. The experience of managing entrapment syndromes exemplifies this, but we recognize that the birth brachial plexus injury represents a potentially more complex scenario. Drs. Pondaag and Malessy suggested a trial that randomizes children to plexus exploration alone or to exploration with external neurolysis. In the absence of demonstrating additional risk by performing external neurolysis, we would be reluctant to enroll patients. Similarly, a study randomizing patients to an external neurolysis group or a resection/grafting group would also be instructive, but the issue there is that children who might benefit from neurolysis but who undergo grafting instead will experience months of potentially negative impact on their development while waiting for reinnervation to occur.

Intraoperative Neurophysiology

The purpose our study was not to establish a “gold standard” or cutoff value for intraoperative neurophysiological evaluation for distinguishing between mainly axometameric and mainly neurometic neuromas-in-continuity. Instead, we intended to present the outcome of infants with infantile brachial plexus palsies (IBPP) with “largely conducting” neuromas-in-continuity as defined by Laurent and Lee.7 Differences may occur when using CMAPs as a means of intraoperative monitoring in our patient population (mean age 10 months, median age 8 months) as compared to Laurent’s population of infants (mean age 5 months, range 2–6 months). A positive correlation exists between CMAP amplitude in infants with IBPP and age; 8 this finding is expected as more of the regenerating axons are reaching their end target. Following serial electrodagnostic examinations over 3 months in a cohort of 48 children with IBPP referred to their center, van Dijk and colleagues9 noted that fibrillation potentials peaked at 55% in biceps muscles and 66% in deltoid muscles at 1 month and diminished to 23% and 14%, respectively, at 3 months. Similarly, motor units were absent 55% of the biceps muscles and 60% of the deltoid muscles at 9 days, and motor units diminished to 2% and 14%, respectively, by the 3-month visit. As expected, polyphasic potentials increased with the onset of reinnervation. The greatest changes in these parameters occurred between the 1- and 3-month visit. Hence, the majority of reinnervation occurred by 3 months. We would therefore anticipate that using CMAPs in our population group would have at least an equal or greater likelihood of reflecting the actual percentage of regenerating axons conducting across the neuroma to their end target. In a less mature group of infants, the measurement of nerve action potentials (NAPs) may be a more appropriate measure of nerve function.

Nerve action potentials have been useful in identifying early reinnervation across the injury site.4 Nerve action potentials with proximal stimulation require regrowth of axons across the lesion site, which is indicative of successful reinnervation. Compound motor action potentials with proximal stimulation, however, require both regrowth of axons and successful reinnervation to the target muscle. Given our older population, we chose to use CMAPs for our intraoperative assessment. Recording CMAPs has the advantage of an amplification of response as each axon innervates and activates hundreds to thousands of muscle fibers. Due to the larger size of the electrical potential, it is less susceptible to problems with excessive stimulus artifact and electrical interference. To determine both the functional continuity and a more precise location of the peripheral nerve lesion, stimulation and recording on either side of the neuroma are suggested.1

Comparing proximal to distal CMAPs across the neuroma does not, nor was it ever intended to, measure axonal loss. Instead, the intent is to determine the proportion of functioning axons or conductivity across the lesion. Visual inspection is important for confirming spinal nerve root avulsion. Extensive nerve thickening, abundant fibrosis, and loss of fascicular continuity strongly suggest neuromatosis. However, as Crum and Strommen have written, “There is no visual way to reliably determine physiological continuity of axons, especially regenerating ones.”3

The work of König et al. cannot be directly compared to the present study. For König and colleagues, external neurolysis was performed if a recordable compound NAP (CNAP) was obtained with proximal stimulation. This criterion is in question because CNAPs have been recorded in infants with IBPP who have lesions classified as avulsions or neuromatosis.8 In the König and colleagues study, lesion severity may have been underestimated. Therefore, infants who would have undergone neuroma resection and grafting in our study may have been mistakenly assigned to the neurolysis group in the König and colleagues study due to the presence of a CNAP.

Chin and colleagues2 measured CMAP recordings after direct proximal and distal stimulation. Motor unit morphology with direct stimulation was used as well as the absence or presence of spontaneous activity. The absence of spontaneous activity and normal morphology of motor units would suggest a conduction block, which would be favorable. Profuse spontaneous activity and few motor units with polyphasic potentials would suggest unfavorable axonal damage with limited reinnervation. The final decision on severity was made using both the results of electrical nerve stimulation and electromyography findings together. Amplitude criterion was also included in their analysis. The results of CMAPs cannot be directly compared with those of our study because Chin and colleagues used concentric needle intramuscular electrodes for recording. While concentric needle recordings would be the most appropriate choice for recording spontaneous activity and the assessment of motor unit morphology, it is not the best choice of electrode for CMAP recording. Compared to surface and subcutaneous needle electrodes, concentric needle electrodes record only from a small part of a muscle and therefore reflect activity in a fraction of the axons that might be stimulated intraoperatively.1 Despite
studies alone.8,10 Electrodiagnostic studies as well as electrodiagnostic evidence of severe IBPP (flexion paralysis at 3 months) may be discovered to have avulsions and neurotmesis based on CMAP or CMAP for predicting a severe lesion was low (< 0.3). Nerve action potentials were recorded in patients who could not be found to differentiate between lesion types in individual patients because of overlapping values. In their quantitative analysis of recordings, the authors determined the cutoff value with the highest likelihood ratio for the CMAP trajectory C-6/biceps to be 0.70 mV, which resulted in a sensitivity of 0.82 and a specificity of 0.82. When the cutoff was set to 0.75 mV, the sensitivity dropped to 0.55. Both NAPs and CMAPs demonstrated a wide numerical range, with the former showing a greater variability than the latter. Given this variability, the ability to measure such a small change in cutoff point would be unrealistic. While the specificity of an absent NAP or CMAP to predict a severe lesion (neurotmesis or avulsion) was > 0.9, the sensitivity of an absent NAP or CMAP for predicting a severe lesion was low (< 0.3). Nerve action potentials were recorded in patients who were discovered to have avulsions and neurotmesis based on visual inspection and lack of significant clinical response to electrical stimulation.

Further work from the Leiden University Medical Center (LUMC) group has demonstrated that the presence of severe IBPP (flexion paralysis at 3 months) may be identified at 1 month of age using clinical factors and electrodiagnostic studies as well as electrodiagnostic studies alone.8,10 Due to the lack of a usable “cutoff” value, the use of quantitative CNAPs and NAPs has been abandoned in the intraoperative assessment of the severity of the brachial plexus lesion in IBPP. The LUMC protocol assigns to the lesion the term avulsion “when the nerve at the intraforaminal and juxtaforaminal level exhibits root filaments, the dorsal root ganglion is visible, neuroma formation is absent, and there is no muscle contraction after direct stimulation.” A spinal nerve is considered neurotmetic when there is “a normal appearance at the intraforaminal level, a clear increase of the cross sectional diameter at the juxtaforaminal level, abundant epineurial fibrosis, loss of fascicular continuity, and increased consistency and increase of the length of the nerve elements with concomitant distal displacement of the trunk divisions. Electrical stimulation of the spinal nerve proximal to the neuroma may cause weak muscle contractions that are detectable with palpation but are not strong enough to move the limb.” A spinal nerve is considered axonotmetic “when neurolysis reveals no substantial increase of the cross section diameter, only limited epineurial fibrosis, and intact fascicular continuity. Furthermore, on C5 stimulation, abduction with movement of the limb and some external rotation should be present, and on C6 stimulation, elbow flexion against gravity with supination should be found.”

The choice of establishing 50% conduction across the lesion as a “cutoff” by Laurent and Lee appears to have been an arbitrary one.6 Recently, a histopathological study of resected neuromas-in-continuity in 28 children with severe nerve injuries and IBPP (median age 5 months, biceps motor strength Grade M0–M1 [British Medical Research Grading system] in 27 of 28 patients) revealed that the mean percentage of regenerating nerve fibers across the neuroma was 41.8% (95% CI 38.7%–44.7%, range 25.3%–58.8%).1 One might speculate that those children who had a less severe lesion and were not chosen for neuroma resection were more likely than not to have greater than 50% regenerating nerve fibers across the neuroma.

The purpose of the present study was not to determine a cutoff point for the decision-making process. The LUMC group has added tremendously to the knowledge of the use of both preoperative and intraoperative neurophysiological assessment of IBPP.7,8,10 It appears that their current practice relies more heavily on the preoperative assessment and the intraoperative appearance of the lesion. Replacement of quantitative NAPs and CMAPs with 3 categories of clinical response to intraoperative electrical stimulation is unfortunate, given their work demonstrating a significant correlation of injury severity with amplitudes of NAPs and CMAPs. Using their current categorization of response to stimulation, however, seems no less arbitrary than Laurent and Lee’s criterion, as there is a lack of a “gold standard” for assessment of the severity of IBPP. Unfortunately, validation of IBPP severity assessments is limited as we are confined to confirming our assessment based on the results of our surgical interventions.

**Functional Recovery and Interpretation**

In our opinion, return of elbow flexion and shoulder abduction/flexion is the hallmark of success for primary nerve surgery. Prior to the advent of nerve transfers, secondary procedures to improve elbow or deltoit function were poor, whereas isolated shoulder external rotation deficiency can be successfully treated, if needed, by tendon transfer surgery, as was performed in 5 of our patients.

**Analysis and Conclusions**

We agree and reported that we did not have complete follow-up, so inclusion bias cannot be completely ruled out. In 7 of the 30 patients who underwent a neurolysis of the upper trunk on primary nerve exploration during our study period of 1999–2008, AMS scores were incomplete at time of data collection. These patients were excluded. Although 5 of the 7 patients were not actually lost to follow-up, at the time of data collection (that is, 2010), they did not have more than 2 years of data collection. Only 2 patients were truly lost to follow-up. There were another 6 patients not included in our data analyses because certain...
characteristics did not fall into the study indications (3 patients had pan-plexus lesions, 1 was treated with upper trunk collagen conduit in addition to adjacent neurolysis, and 2 patients had surgery for reasons other than elbow flexion deficiency). We excluded these 6 to try to keep the cohort as homogeneous as possible to reduce confounding variables. With this potential for inclusion bias in mind, we still think the analysis is a valuable one and one worth reporting.

We agree that inclusion bias cannot be ruled out from Waters’s natural history study. Our complete follow-up rate was 76.7% (23 of 30 patients) compared to Waters’s rate of 70.9% (66 of 93 patients). Both his and our institutions are tertiary referral centers covering large geographic regions.

In response to the fact that we discredited Clarke’s results in his neurolysis-alone group of 8 patients because of its limited size while using Waters’ natural history cohort of 7 patients to our advantage, it should be noted that we used what was available in the literature for a natural history comparison. With today’s generally agreed upon consensus that primary nerve exploration is indicated if the patient shows no antigravity biceps function by age 6 months, there would have been no ethical way to randomize patients into neurolysis-alone and observation-alone treatment arms. In addition, our operative group on average was 10 months old (range 6–19 months), so the prospect that these injuries would have spontaneously improved at this age would have been unlikely. To review, when left untreated, Waters showed that 0 of 7 patients regained hand–mouth function at final follow-up when the biceps function had started to return by 6 months of age. This is in comparison to our treatment strategy: 14 of 16 patients treated with neurolysis alone showed > 90° of active biceps motion against gravity at final follow-up. We realize this comparison is not perfect, but it was used the resources available to try to help navigate this heterogeneous problem.

Neurolysis alone, when employed in the right electrophysiological condition, is one of the treatments that our group has found effective. We think for the weaknesses that Drs. Pondaag and Mallessy have aptly pointed out, there are many significant and valid points in our analyses to justify its continued use in our clinical practice.

**References**


Please include this information when citing this paper: published online July 4, 2014; DOI: 10.3171/2014.3.PEDS14163. ©AANS, 2014