Optimal Effect of Phenol Block in the Sciatic Nerve of Rats: Standardization of Minimized Dosage and Duration of Application

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Abstract

The phenol nerve block has been widely used in clinical practice for spasticity reduction, but the correlation between the dosage of phenol and its effectiveness has seldom been discussed. The objective was to determine the optimal duration of phenol in contact with the nervous tissue and to investigate the dose-response relationship of 5% aqueous phenol solution by percutaneous nerve block in rats. Group I ($n=8$) received sciatic nerve block by bathing the nerves in phenol solution, and group II ($n=40$) by injecting phenol percutaneously. Group IIa to IIId received different volumes (0.80, 0.16, 0.08 and 0.04 ml) and group IIe received normal saline. Compound muscle action potential (CMAP) was measured pre-injection and at 90 and 270 sec after injection and after surgical exposure of the nerves. The duration of CMAP reduced by 10%, 25%, 50%, 75% and 100% after phenol injection was also recorded. The mean latency for the evoked response to subside in direct phenol application (group I) and percutaneous nerve block (group IIa) were $73.5 \pm 5.9$ and $62.4 \pm 7.6$ sec, respectively. There was no statistical difference for the time periods in the blocking effect elicited by phenol solution between these two methods. Ninety sec was set as the optimal duration for phenol to produce complete conduction blockage. Higher volume of phenol produced more significant blocking effect at 90 and 270 sec after injection. Percutaneous injection with 0.16 ml of phenol solution had the same blocking effect as 0.8 ml. The continuous injection model for percutaneous phenol block indeed used significantly more phenol than actually needed. Clinically, the progressive injection model can be used to minimize injection volume.

Key Words: nerve block, nerve stimulation, neurolysis, phenol, rehabilitation, spasticity

Introduction

Spasticity has been defined as disordered sensori-motor control resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles (11). Its manifestation is due to the loss of descending inhibition from the supraspinal structures, and it is one of the most intractable medical conditions in patients with central nervous system disorders. Spasticity may lead to joint contractures and interference with the motor function. Alleviation of spasticity in patients with...
various pathologies is a challenge in clinical neurology. There are, so far, several advances in clinical practice, including the usage of intrathecal baclofen pump, selective dorsal root rhizotomy, botulinum toxin injection and phenol nerve block (4, 14, 18). Phenol nerve block has been used in clinical practice to manage spasticity for more than 40 years (16). It decreases spasticity through non-selective axonal degeneration of peripheral nerves, which are components of the stretch reflex arcs (9, 12). Although botulinum toxin injection is more commonly used to manage spasticity, the number of muscles that can be treated in one visit is limited by the dosing recommendations (7). Combinations of phenol and botulinum toxin injections have been used to manage a larger number of spastic muscles. Phenol nerve block is also effective in larger muscle groups, such as biceps brachii and gastrocnemius muscles, which are innervated by motor nerves. Besides, the motor nerve block can be precisely performed, is time-saving, and is devoid of any complications, as in the case of peripheral nerve block. Although the phenol nerve block, a least expensive and effective therapeutic, has been widely used in clinical practice, the correlation between the dosage of phenol and its effectiveness in spasticity reduction has seldom been discussed in the literature (2). Since the amount of neural damage depends on the dosage of the phenol solution used, the relationship between dose application and effectiveness of phenol nerve block should be established. The goal of this study was to investigate the dose-response relationship of 5% aqueous phenol solution on the sciatic nerve conduction block, following direct application or percutaneous injection of phenol.

Materials and Methods

Animal Preparation

Forty-eight adult male Wistar rats weighing approximately 180-300 g were used. Animals were randomly divided into six groups, 8 rats in each group. The animal experiments were approved by the National Science Council of the Republic of China (NSC 1997). Animal care was in accordance with the guideline of the National Institutes of Health Care and Use of Laboratory Animals (NIH Publications No. 80-23). All efforts were made to minimize animal suffering and the number of animals used throughout the experiment. On the day of experiment, rats were generally anesthetized with intramuscular injection of ketamine (50 mg/kg) and xylazine (10 mg/kg). The rats were monitored for corneal reflex and a response to noxious stimulation to the paw throughout the experiment. If either was present, intermittent ketamine injection was given to maintain anesthesia. At the end of the experiment, the animals were sacrificed by intracardiac saturated potassium chloride solution under deep anesthesia. Sciatic nerves were blocked by bathing in 5% aqueous phenol solution (group I, n = 8), or by injecting the phenol solution percutaneously under the guidance of electrical stimulation (group II, n = 40). The phenol solution was made as previously described (1). Group II was further divided into 5 subgroups, designated as IIa-IIe, according to the volume of injected phenol (Fig. 1).

Direct Phenol Application

Group I rats were treated with 5% aqueous phenol solution by open nerve block. Open nerve block was performed in a small fabricated trough that held...
approximately 0.1 ml of solution to encircle the sciatic nerve, as previously described by Sung et al. (14). The trough was made of a polyethylene tube (length, 1 cm; diameter, 0.5 cm) that was incised longitudinally. A curved mosquito forceps was used to spread out the trough and to transform its tubular shape into a flat sheet. After surgical exposure of the sciatic nerve, the trough was inserted beneath the sciatic nerve. When the mosquito forceps were removed, the trough returned to its original tubular form, encircling the sciatic nerve. The lower end of the trough was packed with wax. Then, 0.02 ml of 5% aqueous phenol solution was dropped into the trough to cover the nerve completely. Stimulation electrodes were placed on the main trunk of the nerve and recording electrodes were placed on the mid belly of the gastrocnemius muscle. A square wave pulse current with a duration of 0.1 ms was applied to the sciatic nerve using a stimulator (Grass S88, Natus Medical Inc., Warwick, RI, USA) connected through a stimulus isolation unit (Grass SIU5B) and a constant current unit (Grass CCU1A). The stimulation parameters were adjusted to obtain a constant compound muscle action potential (CMAP) under continuous stimulation. The filter setting was 10 to 100,000 Hz. The CMAP of the gastrocnemius muscle was recorded after 8 to 12 supramaximal stimuli. Peak to peak amplitude was measured for calculating the maximal CMAP amplitude. The time required for the CMAP amplitude to decrease by 10% (beginning to decline), 25%, 50%, 75% and 100% (totally absent) was recorded. The data were displayed as mean latency ± standard error of the mean, while the optimal duration for the phenol block effect was determined at approximately the mean plus twice the standard error.

**Percutaneous Nerve Stimulation**

In group II, the surface landmark of the sciatic nerve was first determined. Using electrical stimulation to isolate the sciatic nerve, a 27 G Teflon-coated injection needle (TECA Myoject, Viasys Healthcare Inc., Madison, WI, USA) was inserted percutaneously. The needle tip positioning necessary to obtain the maximum CMAP amplitude by the minimal stimulation intensity required was carefully adjusted. After a maximal muscle contraction was achieved by using minimal electrical current, the teflon-coated injection needle was used to inject phenol solution continuously until the CMAP amplitude completely disappeared. The injected volume of 8 samples (group IIa) was averaged and defined as the maximal volume. Twenty percent (group IIb), 40%, 60% and 80% of the above maximal volume of phenol solution was injected to the other four groups of rats percutaneously at a rapid rate after electrical localization of the sciatic nerves. The electrical stimulation was then turned off immediately. After an adequate duration, as determined in group I rats, the electrical stimulator was turned on and the CMAP amplitude of the gastrocnemius muscle was continuously recorded to determine the dose-response relationship. The CMAP amplitude at 3 min after the above duration was recorded for comparisons. Finally, the sciatic nerve was exposed surgically 10 min after the time of injection and observed to determine if the CMAP amplitude was still present under electrical stimulation. However, after injection with 20% of the above maximal volume of phenol solution, CMAP of all the tested sciatic nerves were completely abolished after the previously determined optimal duration. The injection volume was down-adjusted to 20% (group IIb), 10% (group IIc) and 5% (group IIId) of the above maximal volume (as obtained in group IIa), and if a dose-response relationship existed between 5% aqueous phenol solution and sciatic nerve response of the rat was determined.

Finally, 8 rats which received percutaneous normal saline (group IIe) injection served as controls. The three post-injection periods included the optimal duration of phenol block effect, 3 min after the above duration, and 10 min after the time of injection.

**Statistical Analysis**

Results were analyzed by SPSS software (Version 12, SPSS Inc., Chicago, IL, USA). All the data are expressed as mean values ± S.E.M. Wilcoxon rank sum test was used to compare the duration of CMAP reduction by 10% (beginning to decline), 25%, 50%, 75%, and 100% (totally absent) in group I and IIa. Wilcoxon signed rank test was used to compare the amplitude of the evoked response recorded after normal saline injection (group IIe) with the baseline CMAP before injection. For comparison between time periods, a one-way ANOVA using Bonferroni’s post hoc correction for multiple comparisons was used. Fisher exact test was used for statistical analysis to evaluate the existence of the gastrocnemius muscle CMAP between different percutaneous injection volumes in 3 post-injection periods. A P-value of less than 0.05 (two-tailed) was considered as statistically significant.

**Results**

**The Optimal Duration of Phenol Block**

In group I, the minimal current to evoke a maximal CMAP was 0.09 ± 0.01 mA (n = 8). The minimal current intensity was used to continuously evoke CMAPs at a pulse rate of 1 Hz and was recorded as the baseline CMAP. The baseline CMAP held a
relatively constant amplitude during the recording period of 5 min. After the fabricated trough was placed underneath the sciatic nerve, phenol solution (5%, 0.02 ml) was injected into the lumen of the trough. The CMAP was then once again evoked using impulses with the identical stimulation parameters, as in the baseline conditions, for 5 min. A gradual decrease in the amplitude of CMAP was observed after the application of phenol solution. The mean latency for the amplitude of the evoked response to decrease to 90% and 50% of the baseline CMAP, and to be totally absent were 22.50 ± 2.79, 46.00 ± 5.98 and 73.50 ± 5.94 sec, respectively. Ninety seconds was, therefore, determined as the optimal duration of exposure to 5% aqueous phenol solution in rat sciatic nerves. This was based on the calculation of the mean latency required for abolishing the CMAPs plus twice the standard error (i.e., 73.50 + 2 × 5.94 sec). In addition, the absence of an evoked response at 270 seconds (three times the optimal duration) following phenol injection was further confirmed.

Dose-Response Relationship

In group II, a stimulation/injection needle was used to inject phenol solution and deliver electric pulses of varying intensity to percutaneously stimulate the sciatic nerve. The average minimal current intensity that induced the maximal CMAP amplitude was observed to be 0.54 ± 0.04 mA.

The mean injected volume required to completely abolish CMAP in group IIa was 0.80 ± 0.02 ml (n = 8). Four doses, i.e., 0.80, 0.16, 0.08 and 0.04 ml which corresponded to 100%, 20%, 10% and 5% of the maximal volume, respectively, were tested in this experiment. In group IIa, 0.80 ml of the phenol solution was injected percutaneously into the sciatic nerve after establishing a baseline CMAP by impulses (1 Hz) at the minimal current intensity. The amplitude of the evoked response decreased gradually following phenol injection (Fig. 1). The mean latency for the amplitude of the evoked response to decrease to 90%, and 50% of the baseline CMAP, to being totally absent were 17.88 ± 3.68, 33.13 ± 3.64 and 62.38 ± 7.64 sec, respectively. The evoked responses at both 90 and 270 sec following phenol injections were both absent. Direct sciatic nerve stimulation after surgical exposure of the nerve also showed the same results. In group IIc, 0.08 ml of the phenol solution (10% of the maximal dosage) was tested. However, no evoked response was elicited in 2 out of 8 rats at 90 sec, while a total of 5, including the former 2 rats, showed no response at 270 sec after phenol injection. In group IIc, 0.04 ml of the phenol solution (5% of the maximal dosage) was tested. Although a significant reduction in the evoked response was noted, it was not entirely abolished in any of the nerves tested, at either 90 or 270 sec. The amplitude of the evoked response in group IIb showed significant decrease when compared to that in group IIc at 90 sec (P = 0.004, n = 8), and group IIId at 270 sec (P = 0.027, n = 8) following phenol injection (Fig. 3). There was no statistical difference between groups IIc and IIId at either 90 or 270 sec following phenol injection (P > 0.05). Nevertheless, a significant difference in the presence of CMAP was observed in group IIb in comparison with group IIId at each time point measured (P < 0.001; Table 1). The difference between groups IIc and IIId was not significant at 90 sec after phenol injection (P = 0.467), but was significant at 270 sec, and also after the surgical exposure of the nerves (P = 0.026; Table 1).

Vehicle Controls

The amplitude of the evoked response recorded after vehicle injection (0.8 ml saline) showed no
statistical significance \( P = 0.889, n = 8 \) when compared with the baseline CMAP before injection.

**Discussion**

Percutaneous phenol injection has been used in clinical practice to relieve spasticity for more than 40 years (16). The limitation of such a nerve block technique is the nonselective protein denaturation caused by phenol and the risk of associated complications such as dysesthesia, excessive weakness and peripheral edema (5, 10, 12, 15-17). Many factors influence the effect of phenol nerve block, including the concentration and the volume of the injected solution, the selection and localization of the block sites, the duration of contact of phenol with the nervous tissue, and the technique of application (3, 6, 14, 16). Since the optimal duration of phenol in contact with the nervous tissue and the relationship between the nerve block and the injection volume are not yet well established (14), the volume and the duration of injection in current practice mainly depends on the operator’s personal experience. Despite being an inexpensive and effective method to control spasticity, many physicians are hesitant in using phenol-induced nerve block as a feasible treatment option. Therefore, the precise localization of the target nerves and the determination of the optimal dose and duration of phenol in contact with the nervous tissue are crucial. In this study, we recorded the phenol-induced reduction in the CMAP amplitude in rat sciatic nerve following direct application or percutaneous injection of phenol.

Our results indicated that the initial decrease in CMAP occurred at 22.50 ± 2.79 seconds, which was further reduced to one half at 46.00 ± 5.98 sec, and ultimately disappeared at 73.50 ± 5.94 sec. The current results are not in accord with a previous study, where aqueous phenol at concentrations of more than 3% had a constant and immediate effect on nerve conduction block (8). This may be due to the different techniques used in phenol application. The damage caused by percutaneous injection may vary with the site of injection, and can therefore produce different blocking effects (14). In contrast to the percutaneous injection technique, direct application of phenol to the sciatic nerve trunk may achieve a better contact between the agents and the nerve, in which the dosage could be reduced and the injury area could be better defined.

Table 1. Existence of CMAP amplitude after percutaneous phenol injection with 20%, 10% and 5% of the maximal volume

<table>
<thead>
<tr>
<th>Group (Percent of the Maximal Volume)</th>
<th>Existence of the CMAP Amplitude</th>
<th>90 sec</th>
<th>270 sec</th>
<th>Open Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb (20%)</td>
<td>Present</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>IIc (10%)</td>
<td>Present</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>2</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>IId (5%)</td>
<td>Present</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>0</td>
<td>0</td>
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The differences between various groups, as compared using Fisher exact test. CMAP: compound muscle action potential; 90 sec, 270 sec: the duration after phenol injection; Open exposure: surgically exposed sciatic nerve at 10 min after the time of injection.
combined botulinum toxin with phenol to manage spasticity in children and observed visible muscle contractions for about 30 sec after the injection of 0.25 to 0.50 ml of 6% aqueous phenol solution. The procedure was repeated until no further muscle contractions occurred or a total dose of 3.0 ml of phenol was administered. However, in our animal model, we monitored the evoked response following phenol application and the result showed that it took 73.50 ± 5.94 sec for the surgically exposed rats (group I), and 62.38 ± 7.64 sec in the percutaneously injected animals (group IIa), to achieve the nerve blockage after exposure to 5% aqueous phenol solution. Therefore, the optimal duration for phenol in contact with the nervous tissue was suggested to be 90 sec. The protocol used in this study may be beneficial to patients receiving phenol injection, as it significantly reduces the dosage required for a complete nerve block. We suggest that this may, in parallel, minimize the damage area caused by drug injection.

After percutaneous localization of the rat sciatic nerve, injections with 0.08 ml (10% of the maximal volume) of aqueous phenol solution may cause a complete conduction blockage in rat sciatic nerves, but it may take longer contact duration than needed with 0.16 ml (20% of the maximal volume). In groups IIc and IId, the CMAP amplitude varied at the post injection measures. This may be due to the differences in the needle tip and the accuracy of locating the nerve during percutaneous injection, although every attempt was made to approach it by the injection needle under the guidance of electrical stimulation. Using a rabbit model, Sung et al. investigated the distance between the injection needle tip and the nerve during percutaneous nerve block (13). They tested two different stimulation parameters and found that the distance was about 4 mm (-1.2 to +2.8 mm) at 100 μs pulse width and 5 mm (-0.2 to +4.8 mm) at 250 μs pulse width. The average stimulation intensity used in the two groups was 0.47 and 0.37 mA, respectively. In our study, the average electrical current in group II was 0.50 mA, which was similar to the above data. Even with the same volume of phenol, percutaneous phenol injection had different degrees of conduction block. A possible reason for this difference is the variability in the contact area between phenol and the nervous tissue during the manual application of percutaneous nerve block. Therefore, we propose that the needle tip needs to be carefully localized while approaching the nerve closely, and by obtaining the lowest stimulation intensity that may cause some variations in the CMAP amplitude.

In this study, three different methods were used to apply the phenol solution to produce nerve blockage. The volume used in continuous percutaneous injection (group IIa) was 0.80 ± 0.02 ml. However, only 0.02 ml phenol solution was needed to achieve a complete conduction block during the direct application of phenol in surgically exposed sciatic nerves (group I). No statistical difference was observed in the amplitude of the evoked response of these groups at all three post-injection times. Moreover, the volume used in the continuous percutaneous injection group was also higher than that used in the single bolus injection. A single dose of 0.16 ml phenol solution injected percutaneously produced a complete nerve blockage, 90 sec following injection. In addition, using a volume of 0.08 ml (group IIc) had a better chance (5 out of 8) of producing complete conduction block if the injection needle was very close to the targeted nerve. Therefore, we suggest that the volume used in continuous injection to produce nerve blockage should be higher than the volume actually needed. In the present study, we used various dosages of phenol to evaluate the optimal nerve blockage. Our results revealed that percutaneous single bolus injection of phenol solution with a volume of 0.16 ml (20% of the maximal volume) completely blocked the nerve conduction, while 0.08 and 0.04 ml (10% and 5% of the maximal volume, respectively) did not produce a complete blockade. Although a volume of 0.08 ml did block a majority of the sciatic nerve preparations in this experiment (5 out of 8; 62%), it failed to produce nerve blockage in 3 out of 8 (38%) rats. Consequently, we propose that phenol injection with 20% of volume used in continuous injection can produce complete conduction block of sciatic nerve in the rat model. Since this is an animal study, there are some limitations in further clinical application. The size of the injected nerves, the proximity of needle tip to the nerve, and the concentration of phenol solution will have impact on the required volume. Further studies on animal models closer to humans should be done prior to its adaptation to the clinic.

In conclusion, continuous phenol injections during percutaneous nerve block indeed use significantly larger doses of phenol than actually needed. Clinically, we suggest the use of the progressive injection model, which injects a small volume of 5% phenol aqueous solution initially after the proper localization of the target nervous tissue. For the optimal duration of phenol-induced nerve block, we suggest turning on the electrical stimulator to determine if further injection is indicated in order to achieve optimal responses.

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