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Application of Futility Analysis to refine Jitter Recordings in Myasthenia Gravis

Pushpa Narayanaswami, MD¹, Norberto Pantoja-Galicia, PhD², Rebecca A Betensky, PhD², and Seward B Rutkove, MD¹

¹Dept. of Neurology, Harvard Medical School, Boston, Massachusetts

²Dept. of Biostatistics, Harvard School of Public Health, Boston, Massachusetts

Abstract

Introduction—The current practice of single fiber electromyography (SFEMG) requires that 20 fiber pairs with normal jitter be collected to exclude myasthenia gravis (MG). We applied principles of futility analysis from clinical trials in an attempt to reduce that requirement.

Methods—We utilized conditional power futility analysis to assess the probability of an abnormal 20-pair SFEMG based on ongoing analysis of jitter as each pair is collected. Rules for early test termination in the presence of 0, 1 or 2 abnormal pairs were identified. These rules were then applied to previously collected SFEMG data.

Results—SFEMG could be stopped at just 12 pairs if all are normal and at 17 pairs if 1 is abnormal. The rules successfully determined when SFEMG could be stopped in 104/106 (98%) studies originally reported to be normal.

Discussion—If the first 12 SFEMG pairs have normal jitter, the study can be terminated and interpreted as normal.

Keywords

SFEMG; single fiber electromyography; myasthenia gravis; futility analysis

INTRODUCTION

Single fiber electromyography (SFEMG) remains the most sensitive test for myasthenia gravis (MG), which may be excluded if fewer than 10% of collected muscle fiber pairs have increased jitter.^{1–2} No study has specifically addressed how many fiber pairs must be collected during SFEMG. The pivotal multicenter study to establish reference values for SFEMG recommended that 20 pairs be collected.^{1,3} Since SFEMG is time-consuming and uncomfortable, it would be preferable to study the least number of pairs. Some patients tolerate SFEMG poorly, and testing is terminated before collecting 20 pairs. The goal of this study was to minimize the number of pairs without compromising the high sensitivity of SFEMG.¹

Futility analysis is a clinical trial design wherein accumulating results are monitored for futility, the inability of the trial to achieve its objectives.⁴ One such analysis is the

Correspondence and Reprints to: Pushpa Narayanaswami, MD, FAAN, Dept. of Neurology, Harvard Medical School, Beth Israel Deaconess Medical Center, TCC-8, 330 Brookline Avenue, Boston MA 02215, 617-667-4382, Fax 617-667-3175, pnarayan@bidmc.harvard.edu.

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conditional power design, in which the probability of a statistically significant final result, based on currently observed data, i.e., conditional power, is calculated. When this conditional power falls below a pre-defined threshold (the futility threshold), the trial is terminated.⁵ We hypothesized that we could utilize conditional power futility analysis to determine the minimum number of fiber pairs to be collected during SFEMG to exclude MG.

Thus, the study aims were: (1) to utilize futility analysis and derive testing rules so that SFEMG could be stopped when the probability of an abnormal result was sufficiently low, thus excluding MG more efficiently and (2) to assess the validity of the testing rules by applying them to previously collected normal and abnormal SFEMG data.

MATERIALS AND METHODS

After receiving institutional review board approval, the data of all patients who had undergone SFEMG for evaluation of MG between January 1, 2003 and December 31, 2007 were retrieved from the computerized database in the EMG laboratory at Beth Israel Deaconess Medical Center. The patients' online medical records were also obtained.

Jitter analysis is routinely performed in our laboratory on a TECA Synergy T2 EMG machine (Viasys Healthcare, Madison, WI) with a 25mm X 30G concentric needle (TECA Elite disposable needle US53153, recording surface area 0.019mm²) using standard recording methods as described by Stalberg.⁶ Because we use concentric needle electrodes, the low frequency filter is set at 2000 Hz. Stable potentials 100μv with a fast rise time are accepted for analysis.⁷ We define an abnormal study as one with at least 3/20 (>10%) fiber pairs with jitter greater than 95% upper confidence limit of normal in individual fiber pairs. Although published normal reference values derived using single fiber electrodes are used, there is reasonably good concordance between jitter values obtained using concentric needles and single fiber needles.^{1-3,6-12} Concentric needle jitter may be slightly lower, and thus our calculations are likely conservative.⁷

The individual jitter of all fiber pairs for each muscle tested was tabulated. The raw jitter values (continuous data) were converted to categorical data: normal jitter was categorized as 0 and increased jitter as 1. We then utilized a conditional power design model to derive the rules of testing. This design monitors the results of a test as data is being acquired and suggests stopping when the probability of an abnormal result by the end of the study (the conditional power) based on the data obtained up to that point falls below a preset threshold, γ , the futility threshold.

In order to calculate the conditional power (the probability of an abnormal SFEMG if the test were continued out to 20 pairs) at each fiber pair, it is necessary to know the probability that a pair will have increased jitter (p). However, the true probability of an abnormal pair in normal subjects is unknown. In a study of 152 normal subjects aged 10–89 years, Stalberg and Thiele did not find increased jitter in anyone below 60 years of age.¹³ Increased jitter was found in 0.6% of pairs in patients aged 60–68, and in 2.8% of those above age 80.¹³ Since the generally accepted definition for a normal SFEMG study is 10% pairs with increased jitter, we set the probability that a given fiber pair will have increased jitter, $p=0.10$. This is a very conservative estimate for p .¹³ A conditional power analysis was then performed as follows:

Let c_i denote the probability of declaring an abnormal test by the end of the 20 pairs given the findings of pairs 1 to i , for $i=1, \dots, 19$:

$c_i = P \{ \text{declare an abnormal test by the end of 20 pairs given the findings of pairs } 1, 2, \dots, i \}$. A decision to terminate the study will be made when the probability c_i falls below a pre-specified level, the futility threshold, γ . In other words, we stop in favor of futility after the i^{th} pair and declare a normal SFEMG if $c_i \leq \gamma$. Here, we take $\gamma = 0.05$ i.e., the probability that the SFEMG will be abnormal if we were to continue and collect 20 fiber pairs is less than 5%.

The criterion for an abnormal 20-pair SFEMG is ≥ 3 pairs with increased jitter. Therefore, the probability of declaring an abnormal test by the end of the 20 pairs given that “k” abnormal pairs have been seen in pairs 1 to i is:

$c_{i,k} = P(\geq 3 \text{ abnormal pairs by pair 20 given that } k \text{ abnormal pairs have been seen in pairs } 1, \dots, i) = P(\text{see } \geq 3 - k \text{ abnormal pairs in pairs } i+1, \dots, 20 \text{ given that } k \text{ abnormal pairs have been seen in pairs } 1, \dots, i)$

Or:

$c_{i,k} = P(X_{i+1,20} \geq 3 - k | X_{1,i} = k)$, where $X_{m,n}$ denotes the number of abnormal pairs seen in pairs m to n, $i = 1, \dots, 19$ and $k = 0, 1, 2$. It is assumed that $X_{m,n}$ is distributed according to a binomial distribution with parameters $(n - m + 1, p)$. Here, $n - m + 1$ is the number of pairs from pair m to pair n, and p represents the probability that a pair is abnormal, for example $p = 0.1$. We also assume that pairs are independent within a muscle, i.e., $X_{i+1,20}$ and $X_{1,i}$ are independent and that patients are independent and p is constant for all pairs.

In summary, at each fiber pair, i, the probability of finding $>10\%$ (i.e. 3 or more of 20) abnormal fiber pairs if the next (i-20) pairs are collected is calculated. For example, at the 5th fiber pair, if all pairs are normal, the probability of finding 3 abnormal fiber pairs in the next 15 pairs is computed. If there are 1 or 2 abnormal fiber pairs in the first 5, the probability that the next 15 pairs will have 2 or 1 more abnormal pairs, respectively is calculated. This probability $c_{i,k}$ is conditional upon what has been observed up to pair i. The threshold probability below which we would be willing to stop the study and accept the false negative error rate is the futility threshold, $\gamma = 0.05$. As each fiber pair is acquired during SFEMG, the calculated conditional power $c_{i,k}$ is compared to the chosen futility threshold γ . When $c_{i,k} \leq \gamma$, it is futile to continue the study. In the example above, at the 5th pair, if $c_{5,k}$ is sufficiently low, say, 0.04, it would mean that given the jitter in pairs 1–5, the probability of an abnormal SFEMG even if the next 15 pairs were collected is only 4%. Since this is below our preset futility threshold, γ , of 0.05, it would be “futile” to continue the test, and the SFEMG is terminated and called normal after just 5 pairs are collected.

In addition to $p = 0.1$, we selected two other methods for estimating p, similar to that proposed by Pepe and Anderson (PA).¹⁴ In contrast to the previous approach, where $p = 0.1$ remains constant at every pair, with the PA multi-stage statistical method, the conditional probability $c_{i,k}$ is obtained at each pair by a sequential computation of the data from all earlier pairs, thus updating p for every pair constantly as each consecutive pair is analyzed. In order to do this, exact one-sided binomial confidence intervals (CI) were calculated around p. Two PA settings for p were used: **PA 84%** and **PA 65%** which were the upper confidence limits of an exact binomial one-sided 84% CI and 65% CI respectively. Since probability is positive and the data are binomially distributed, only one-sided CIs are relevant. The upper confidence limit takes into account the fact that the point estimate p is likely to vary, especially early in the study. Using a 95% CI would be overly conservative and would make stopping for futility unlikely. The upper 85% and 64% confidence limits were chosen as representing a more conservative estimate of the truth than the upper 95%

confidence limit. Data-driven values for p using these upper confidence limits, re-estimated after each pair was collected were thus obtained.¹⁴

Thus, conditional power analyses were performed with each of the 3 settings for p ($p=0.1$, $p=PA\ 84\%$, $p=PA\ 65\%$) under 3 possible circumstances: 1) No fiber pairs with abnormal jitter; 2) One pair with increased jitter; 3) Two abnormal pairs were obtained. This conditional probability was calculated at each pair given the number of abnormal pairs up to that point: 0, 1 or 2; hence it did not matter which pair was abnormal: the first or any subsequent pair.

RESULTS

Futility analyses

Applying the conditional power analysis discussed above, (Table 1) indicates the conditional probabilities of an abnormal 20 pair-SFEMG, given the number of abnormal pairs (0, 1 or 2) as each pair is acquired. This table also indicates where we would stop in favor of futility and declare the SFEMG normal (the pair at which $c_i - \gamma = 0.05$). Therefore Table 1 is the probability reference table denoting the rules for testing. Figure 1 shows the consecutive probabilities of an abnormal SFEMG as each pair is collected for $p=0.1$. Similarly for $p=PA\ 84\%$, the consecutive probability of an abnormal SFEMG falls below 5% at the 14th pair if all fiber pairs have normal jitter, and at the 18th pair if there is one pair with abnormal jitter. (Supplementary Figure.1). In summary, the *Rules of Testing* are:

1. If there are no abnormal fiber pairs, the SFEMG can be stopped at 11, 12 or 14 pairs and be called normal for settings of $p=PA\ 65\%$ [updating p], 0.1 [fixed p] and $PA\ 84\%$ [updating p] respectively, because the probability of an abnormal SFEMG even if carried out to 20 pairs is 5%.
2. When 1 abnormal pair is acquired, the SFEMG can be stopped at 17 ($p=0.1$ or $PA\ 65\%$) or at 18 pairs ($p=PA\ 84\%$) and be reported as normal.
3. When 2 abnormal pairs are acquired, the probability of an abnormal SFEMG remains $> 5\%$ even at 20 pairs; therefore, the study will be continued.

Application of the rules of testing to previous SFEMG data

Between January 1, 2003 and December 31, 2007, 191 SFEMG studies were performed. Data were available for 163 studies. All normal studies with 20 or more pairs and all studies reported as abnormal were included in the analysis. Five studies were reported “borderline” or “inconclusive”. One study was excluded because it was technically limited. Of the remaining 4, 1 study was normal, but MG was confirmed in another muscle. The patient had ocular MG clinically. Another study had 1 of 20 abnormal pairs and was reported as “borderline,” because the jitter in that pair was markedly elevated (108 μ sec, normal 35.5 μ sec). The other 2 had 2 of 20 pairs with abnormal jitter. Since all four studies met criteria for normal SFEMG at 20 pairs they were considered to be “normal” for the purpose of this analysis (sections b and c below) Data from 130 muscles were available for the final analysis. Of these, 106 (81%) studies in 104 patients were ultimately categorized as normal, and 24 muscles in 23 patients (18%) were categorized as abnormal by the full 20-fiber pair SFEMG.

a) Testing Rules applied to studies without abnormal fiber pairs—No abnormal pairs were acquired in 91 of 130 (70%) studies. According to the testing rules, the SFEMG could be stopped and be called normal after 11, 12 or 14 pairs were collected (for settings of $p=PA\ 65\%$, 0.1 and $PA\ 84\%$, respectively). Continuing the test to 20 pairs did not change

the SFEMG findings. Thus, the SFEMG results obtained by applying these rules were fully concordant with the results of the 20- pair SFEMG.

b) Testing Rules applied to studies with one abnormal fiber pair—There were 13 of 130 (10%) studies with 1 abnormal pair. In all 13 studies, the percentage of abnormal pairs fell below 10% well before the 17th pair, and no further abnormal pairs were seen. Hence the SFEMG could be stopped at the 17th pair and be called normal without missing an abnormal study. Thus, SFEMG results obtained by applying these rules were fully concordant with the results of the 20-pair SFEMG.

c) Testing Rules applied to studies with two abnormal fiber pairs—Two studies (2%) had 2 pairs with elevated jitter. Since the rules of testing state that when 2 abnormal pairs are acquired during the study, the probability of an abnormal SFEMG remains > 5% even at 20 pairs, these studies would not have been considered to be normal. In practice, more fiber pairs would have been acquired to clarify whether the study met criteria for abnormality. The full 20-fiber pair SFEMG in these 2 cases was interpreted as “borderline normal”, because one pair in each had a very elevated jitter. Importantly, no further abnormal pairs were found in the one study in which 20 pairs were obtained nor in the second in which 29 pairs were obtained. Both these patients were also not thought to have MG clinically after follow up of 27 months and 6 months respectively (diagnoses: cranial neuropathy, orthostatic hypotension). Thus, in 104 of 106 normal studies (98%), the stopping rules were concordant with the results of the full 20-pair SFEMG.

d) Testing Rules applied to studies with more than 2 abnormal fiber pairs—Twenty- four of 130 studies (18%) had more than 2 abnormal pairs and were reported to be abnormal on the original SFEMG report. Twenty-two of 24 studies had at least 1 abnormal pair before pair 11 and fulfilled SFEMG criteria for abnormality by pair 17 of 18 (Table 2). In 2 of 24 studies, all initial fiber pairs were normal: 1 until pair 15, the other till pair 11. The first study would have been stopped and been called normal at 11, 12 or 14 pairs (discordant with the 20-pair SFEMG). The mean jitter was mildly elevated (46.01 μ sec, normal 40 μ sec), and nerve conduction studies revealed a mild chronic axonal polyneuropathy. The clinical diagnosis was inconclusive over 7 months of follow-up. The second study would have been stopped and been called normal by the rules of testing using p=PA 65% at pair 11, but the jitter in pair 12 was increased, with 4 abnormal pairs between pairs 12 and 20. The mean jitter was elevated (47.5 μ sec, normal 40 μ sec). The clinical diagnosis was cranial neuropathy. This study would not have been considered to be normal using the stopping rules with p=0.1 or PA84% at 12 or 14 pairs. Therefore, the SFEMG results using the rules of testing were concordant with the 20-pair SFEMG in 22 of 24 (91%) studies that were ultimately reported to be abnormal with all three settings of p and in 23 of 24 (95%) with p=0.1 or PA 84%. Only 1 of 24 (4%) studies reported ultimately to be abnormal was not concordant with the 20-pair SFEMG. As discussed above, this patient did not have MG clinically.

DISCUSSION

In this study, we have applied the principles of conditional power futility analysis, from the arena of clinical trial design, to SFEMG in order to exclude MG more efficiently. We found that if all fiber pairs have normal jitter, the SFEMG could be stopped at 12 pairs and be called normal with an error rate of < 5%. If there was one fiber pair with increased jitter, we would have to test 17 pairs, a shortening of the test by 40% and 15% respectively. The rules of testing derived using conditional power futility analysis are therefore highly concordant with the full 20-pair SFEMG in determining a study as normal when there are 0 or 1 abnormal pairs. There were only 2 studies with 2 abnormal pairs. Since the rules of testing

state that the probability of an abnormal SFEMG is >5% even beyond 20 pairs, the testing would have been continued. Applying the rules to a larger number of studies with 2 abnormal pairs is necessary before drawing conclusions. The rules of testing were also concordant with the full SFEMG in identifying 23 of 24(95%) of the abnormal studies, and the one discordant study was not consistent with MG clinically. Because this was a retrospective analysis of SFEMG data, only 6 of the studies ultimately called abnormal had 18 or greater pairs. A prospective study that collected 20 fiber pairs in every SFEMG would be useful.

Several limitations of this analysis are worth highlighting. Conditional power analysis depends on the setting of p , the probability that the test will be abnormal, in this case the probability of finding a fiber pair with abnormal jitter. The “stopping rule” is calculated based on the numerical value for this probability. We set this value at 0.1. We also discuss other settings for p , including the Pepe-Anderson method. Further analyses with other settings for p , based either on historical or prospective data may be useful in refining the technique. Secondly, we converted the jitter values, a continuous data set, to dichotomous data. Hence the relative importance of jitter values in the “high normal” range as compared to those that were more robustly normal may be lost in the analysis. This study does not take into consideration the second criterion for an abnormal SFEMG, the mean jitter values. The recommended criterion for an abnormal SFEMG is either: 1) More than 10% of fiber pairs have jitter values that are >95% of the upper limit of normal for single fiber pairs for the muscle and age; or 2) Mean MCD is greater than 95% of the upper limit of normal for the given muscle and age. Mean jitter and individual jitter measurements are usually concordant, except in occasional instances when the mean jitter may be increased with <10% pairs having increased jitter.¹ In all, 18 of 24 abnormal studies where clinical follow-up was consistent with MG, both mean and individual jitters were concordant, and either analysis would have provided the same result. However, as is the case with any diagnostic test, the results need to be interpreted in the light of the clinical context.

In conclusion, this study confirms that conditional power utility analysis may be useful to reduce the number of pairs acquired during SFEMG and thus efficiently exclude a diagnosis of MG. If no pairs with increased jitter are obtained, the study may be stopped at the 12th pair. If one pair with abnormal jitter is obtained, 17 pairs must be analyzed before the test can be declared “normal” and stopped. Larger prospective studies that also apply utility analysis to the second SFEMG criterion for abnormality, the mean jitter, calculated as each fiber pair is acquired, will be useful to develop a composite measure for stopping SFEMG early based on both criteria for an abnormal SFEMG.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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ABBREVIATIONS

CI	Confidence Interval
EMG	Electromyography
MG	Myasthenia Gravis

PA	Pepe- Anderson Method
SFEMG	Single Fiber Electromyography

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Fig. 1. Consecutive probabilities at each fiber pair of an abnormal SFEMG, $p=0.10$

If there are no abnormal fiber pairs, SFEMG may be stopped at the 12th pair with a <5% probability of an abnormal 20 pair SFEMG. When 1 fiber pair is abnormal, the probability that the SFEMG will be abnormal at the first pair is 58% and falls to <5% at the 17th pair, when the test can be stopped. If 2 fiber pairs are abnormal, the probability of an abnormal SFEMG is very high to start with, and remains high (10%) even at the 19th pair. The PA 65% probabilities are very similar (see Table 1).

Table 1

Rules of Testing

Conditional probability of an abnormal SFEMG if 20 fiber pairs are collected, given the ongoing data. For $p=0.1$, if no abnormal fiber pairs are seen, the SFEMG can be stopped at the 12th pair, with less than 5% probability that the full 20 pair SFEMG will be abnormal. If 1 fiber pair has abnormal jitter, 17 fiber pairs must be collected. The bold numbers indicate the fiber pairs at which the SFEMG can be stopped for $p=0.1$, PA 84% and PA 65%, with 0, 1 or 2 abnormal fiber pairs respectively.

pair i*	$\hat{p}$ p=0.10			p=84% PA			p=65% PA		
	$\hat{p}$ k=0	k=1	k=2	k=0	k=1	k=2	k=0	k=1	k=2
1	0.295	0.580		1.000	1.000		1.000	1.000	
2	0.266	0.550	0.850	1.000	1.000	1.000	0.993	1.000	1.000
3	0.238	0.518	0.833	0.997	1.000	1.000	0.917	1.000	1.000
4	0.211	0.485	0.815	0.967	1.000	1.000	0.751	0.999	1.000
5	0.184	0.451	0.794	0.884	1.000	1.000	0.561	0.994	1.000
6	0.158	0.415	0.771	0.755	0.997	1.000	0.395	0.973	1.000
7	0.134	0.379	0.746	0.605	0.987	1.000	0.268	0.927	0.999
8	0.111	0.341	0.718	0.458	0.961	1.000	0.176	0.854	0.997
9	0.090	0.303	0.686	0.330	0.913	0.998	0.112	0.759	0.990
10	0.070	0.264	0.651	0.227	0.840	0.994	0.070	0.650	0.976
11	0.053	0.225	0.613	0.148	0.744	0.985	0.042	0.536	0.952
12	0.038	0.187	0.570	0.092	0.631	0.966	0.024	0.423	0.913
13	0.026	0.150	0.522	0.053	0.508	0.934	0.013	0.319	0.859
14	0.016	0.114	0.469	0.028	0.385	0.883	0.006	0.228	0.788
15	0.009	0.081	0.410	0.013	0.269	0.809	0.003	0.150	0.699
16	0.004	0.052	0.344	0.005	0.168	0.710	0.001	0.089	0.591
17	0.001	0.028	0.271	0.001	0.086	0.581	0.000	0.044	0.467
18		0.010	0.190		0.029	0.420		0.014	0.326
19			0.100			0.227			0.170
20									

* i= number of pairs;

$\hat{p}$ k= number of pairs with increased jitter seen from pairs 1 to i;

p^* = probability of finding an abnormal fiber pair;

s_{PA}^* = updated Pepe-Anderson probability

Table 2

Rules of testing applied to patients with abnormal standard SFEMG

	Number of studies	Mean first fiber pair abnormal (range)	Mean second fiber pair abnormal (range)	Clinical diagnosis
Studies for which the rules were concordant with the 20- pair SFEMG at all three values for p *	22	1.9 (1–6)	4.9 (2–17)	18 (82%) myasthenia gravis, 2 no follow-up, 2 inconclusive after 4 and 5 months follow- up
Study for which the least conservative rules (p=PA 65) were not concordant but other rules (p=0.1, PA 84) were concordant with the 20-pair SFEMG	1	12	13	cranial neuropathy
Study for which the rules were not concordant with the 20- pair SFEMG for any of the 3 values of p	1	16	17	Inconclusive after 7 months of follow-up

* p=probability of abnormal jitter. The 3 values of p were 0.1, PA 84% and PA 65%