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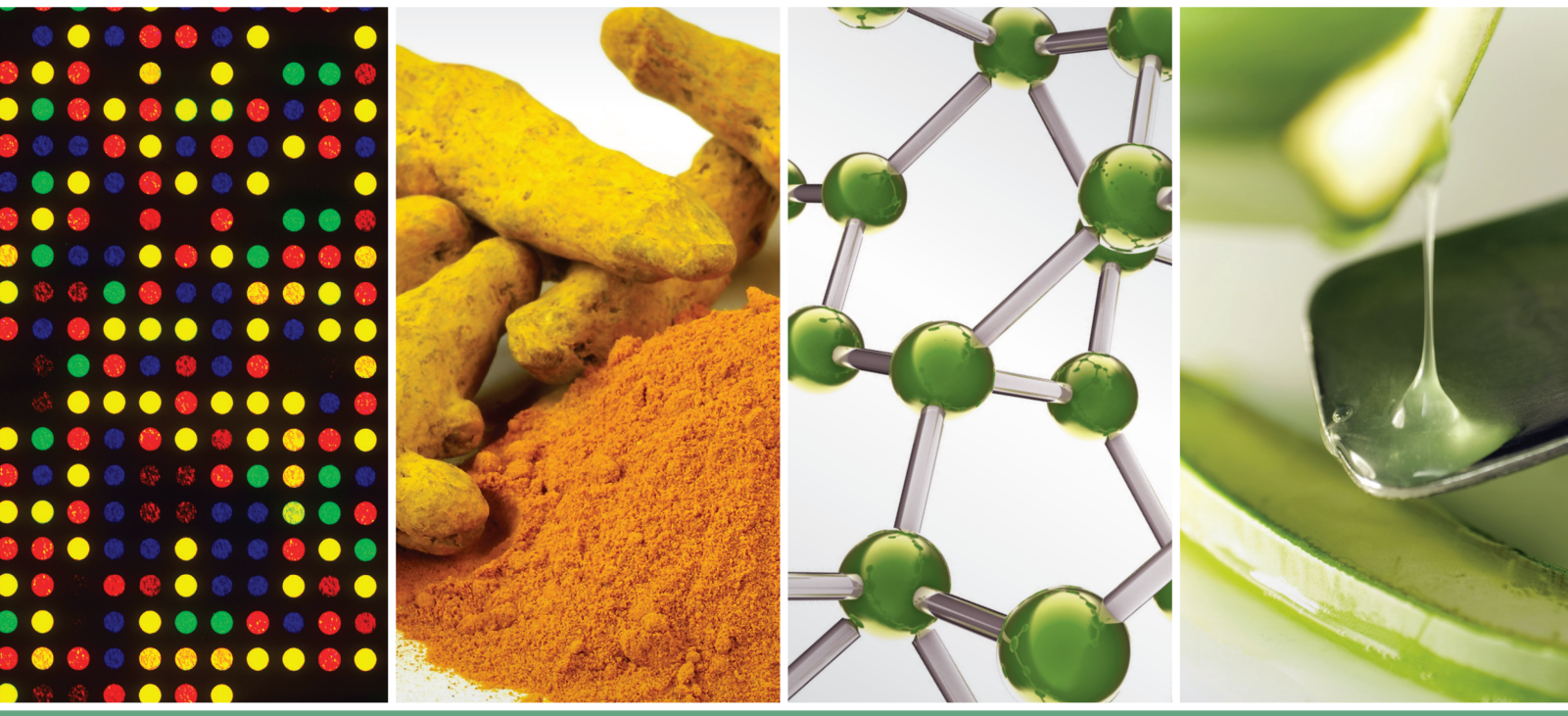
Needling Therapy for Myofascial Pain Control

Guest Editors: Chang-Zern Hong, Marta Imamura, and José M. Climent Barberá



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Editorial Board

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Editorial

Needling Therapy for Myofascial Pain Control

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Needling therapy has been widely used for pain control. "Needling" includes all procedures with penetration of a needle through the skin with injection of medication (injection therapy) or without introduction of any drug (dry needling). In either injection or dry needling, the site of treatment can be at the site of pain (direct needling) or far from the site of pain (remote needling). Needling therapy includes traditional acupuncture, needling with multiple insertions, dry needling with electrical stimulation, superficial needling, and Fu's subcutaneous dry needling.

Myofascial pain is a regional pain syndrome characterized with the existence of a sensitive spot (myofascial trigger point (MTrP)) in the taut band of skeletal muscle fibers. MTrP can be inactivated by appropriate treatment with physical therapy (including manual therapy) or needling therapy.

This special issue contains nine papers, of which two are review articles and seven are research articles. The review paper by L.-W. Chou et al. discussed various proposed mechanisms published previously and concluded that multiple mechanisms are probably involved in needling analgesia. Another review paper by J. M. Climent et al. discussed the clinical trials of botulinum toxin injection for treating myofascial pain in the neck and back, and concluded that botulinum toxin could be useful in specific myofascial pain regions, especially for patients with refractory myofascial pain that has not responded to other myofascial injection therapies. Two clinical studies demonstrated the effectiveness of dry needling in treating myofascial pain after total knee arthroplasty (O. Mayoral et al.) and remote pain in the upper trapezius muscle (K.-H. Chen et al.). One animal study by Y.-L. Hsieh et al. showed that dry needling at the myofascial trigger spots (MTrSs, equivalent to human MTrP) of rabbit biceps femoris muscles could modulate various biochemicals associated with pain, inflammation, and hypoxia in a dose-dependent manner. The other animal study by A. Domingo et al. found that repeated dry needling punctures in muscle do not perturb the different stages of muscle regeneration and reinnervation. Another research study by M.-T. Lin et al. suggested that the artificial neural network (ANN) model was more accurate in predicting patient-reported pain scores and had higher overall performance indices. Finally two papers reported their newly developed techniques for myofascial pain control. An animal study by Fu et al. further confirm the effectiveness and the possible mechanism of Fu's remote needling for myofascial pan therapy. The study by Lin et al. demonstrated the effectiveness of Lin's percutaneous soft tissue release (less invasive than the surgical release) for treating chronic recurrent myofascial pain due to lateral epicondylitis.

Many studies in this issue reported the application of multiple insertion technique for dry needling therapy. In either clinical practice or research studies, it has been suggested that needling with "multiple insertion technique" can usually provide the best and fastest effects for immediate pain control. This technique was originally described by Travell and Bobb for myofascial trigger point (MTrP) injection. During injection, the needle was moved in and out into different directions to elicit painful sensation (to encounter the sensitive loci) in an MTrP region. In this way, MTrP pain can usually be eliminated nearly completely immediately after most of those multiple sensitive loci have been injected (or encountered). Considering the time consuming and the possibility of muscle fiber damage during this slow needle movement, C.-Z. Hong has modified this technique into a "fast-movement procedure" in order to avoid tissue damage

from side movement of needle or grab of needle by the elicited local twitch responses (LTRs). Later, this new technique has been recommended by Simons and has been widely used for MTrP injection or dry needling.

The descending pain inhibitory system is probably involved in the mechanism of immediate pain relief after multiple needle insertion. Either hyperstimulation analgesia for general pain control or disruption of "MTrP" circuit for myofascial pain control is actually via the descending inhibitory system. It has been suggested that eliciting LTRs (feeling similar to "De-Qui" effect) during needling is essential to obtain an immediate and complete pain relief after MTrP needling or MTrP injection. Eliciting an LTR or obtaining "De-Qi" effect indicates that a sensitive locus (sensitized nociceptor) is encountered by the needle tip. It appears that, when a sensitive locus is encountered by the tiny needle tip, "De-Qi" effect can be perceived and an LTR can be elicited, and then the irritability of this sensitive locus can be suppressed immediately. Needling of a key MTrP can also inhibit the irritability of satellite MTrPs due to central desensitization phenomenon. It is important to provide strong stimuli to the sensitive loci as many as possible to obtain optimal hyperstimulation in order to have maximal pain relief; so that the "multiple insertion technique" can provide better effects than just a single site stimulation.

Based on the reports in this special issue, it is very likely that the above issues have been further clarified.

Chang-Zern Hong

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Research Article

Comparisons of Prediction Models of Myofascial Pain Control after Dry Needling: A Prospective Study

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Background. This study purposed to validate the use of artificial neural network (ANN) models for predicting myofascial pain control after dry needling and to compare the predictive capability of ANNs with that of support vector machine (SVM) and multiple linear regression (MLR). *Methods*. Totally 400 patients who have received dry needling treatments completed the Brief Pain Inventory (BPI) at baseline and at 1 year postoperatively. *Results*. Compared to the MLR and SVM models, the ANN model generally had smaller mean square error (MSE) and mean absolute percentage error (MAPE) values in the training dataset and testing dataset. Most ANN models had MAPE values ranging from 3.4% to 4.6% and most had high prediction accuracy. The global sensitivity analysis also showed that pretreatment BPI score was the best parameter for predicting pain after dry needling. *Conclusion*. Compared with the MLR and SVM models, the ANN model in this study was more accurate in predicting patient-reported BPI scores and had higher overall performance indices. Further studies of this model may consider the effect of a more detailed database that includes complications and clinical examination findings as well as more detailed outcome data.

1. Introduction

Myofascial pain syndrome (MPS), a common cause of musculoskeletal pain presenting in primary care, results from myofascial trigger point activity [1, 2]. Dry needling is a treatment modality that is minimally invasive, cheap, and easy to learn with appropriate training and carries a low risk. Its effectiveness has been confirmed in numerous studies and comprehensive systematic reviews [3–5]. Accurately predicting myofascial pain control, a standard outcome measure after dry needling, is important when selecting treatment modality and when allocating scarce medical resources [1, 2].

Regression analysis, one of the most widely used multivariate analysis methods, assumes linear relationships between independent and dependent variables. However, studies show that changes in biomedical variables are often nonlinear [6–10]. The major classifier methods use support vector machines (SVMs) to solve classification problems by constructing hyperplanes in a multidimensional space that separates cases of different class labels. However, SVMs have also been proven effective for solving regression problems because they can handle multiple continuous variables [6–10]. Artificial neural networks (ANNs) are complex and flexible nonlinear systems with properties not found in other modeling systems. These properties include robust performance in dealing with noisy or incomplete input patterns, high fault tolerance, and the capability to generalize from the input data [6–10]. The computational power of an ANN is derived from the distributed nature of its connections. The ANN model is a well-established data mining algorithm that is widely used in various fields, from engineering to biomedical science [6–10].

The multilayer perceptron (MLP) is the most frequently used ANN due to its ability to model nonlinear systems and establish nonlinear decision boundaries in classification problems such as optical character recognition, data mining,

and image processing/recognition [11, 12]. Our chosen model in the present study was a multilayer perceptron network, and we focus on the MLP type of ANN, the most common type.

Despite their contribution to the growing understanding for predicting myofascial pain control after dry needling, previous studies of dry needling outcome have had major shortcomings [13–15]. Few studies of dry needling outcome have used longitudinal data for more than one year. Moreover, no studies have considered group differences in factors other than outcome such as age and nonsurgical treatment. Additionally, almost all published articles agree that the essential issue of the internal validity (reproducibility) of the ANN, the SVM, and multiple linear regression (MLR) models has not been adequately addressed.

Therefore, the primary aim of this study was to validate the use of ANN models in predicting patient-reported quality of life (QOL) after dry needling, and the secondary aim was to compare the predictive capability of ANNs with that of SVM and MLR models.

2. Materials and Methods

2.1. Ethics Statement and Study Population. The subjects included all MPS patients who had been referred for evaluation and treatment to the Pingtung Christian Hospital (PTCH) pain clinic from February to October, 2008. Inclusion criteria were chronic musculoskeletal pain for three months or longer due to nonspecific muscle pain, physical examination revealing tender spot in a palpable taut band, ability of a patient to distinguish between varying intensity of pain, referred pain pattern and local twitch response, Chinese speaking, and age at least 18 years. Exclusion criteria were fibromyalgia syndrome, neurological pain, infection, drug or alcohol abuse, rheumatologic disease, pregnancy, and any other disease that might interfere with participation ($n = 18$). The research protocol was reviewed and approved by the institutional review boards of PTCH. Of the 439 eligible subjects who gave written consent and were enrolled in the study at baseline, thirty-nine patients were excluded due to loss of contact. All 400 of myofascial pain control after dry needling subjects completed the pretreatment and 1-year posttreatment assessments (Figure 1).

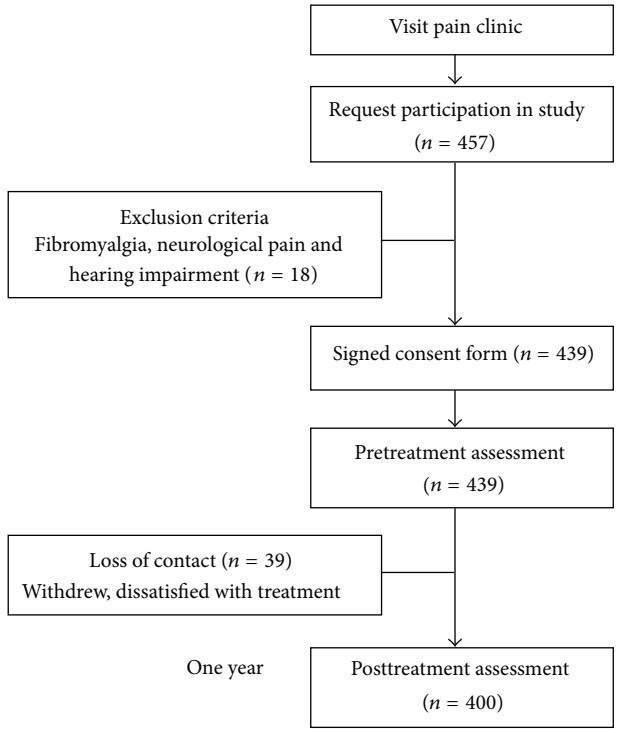

Figure 1: Progression of participants through the trial, including those who met exclusion criteria, those who withdrew, and those who were lost to followup.

2.2. Interventions. All needling protocols were performed by a single specialist. Taut bands with trigger points were isolated by palpation to ensure reproducibility of symptoms. Therapeutic needling was then performed with sterile 32G-diameter, 80 mm acupuncture needles. A needle plunger was first used to pierce the skin and muscle with the acupuncture needle. After the needle penetrated the skin, the plunger was removed, and the needle was inserted further into the taut band to elicit a twitch response. Appropriate placement of the needle was confirmed by reproduction of recognizable pain or by observation of local twitch response. The needle was then partially withdrawn and repeatedly inserted into the muscle until no further twitches were observed. After inactivating trigger points and reducing referred pain, the specialist then passively stretched the involved muscle toward its normal length. The patients then performed the muscle-stretch exercise technique developed by Travell and Simons [16]. All subjects received eight needling protocols administered over an 8-week period and no other treatment was given in the next months after 8-week dry needling.

2.3. Instruments and Measurements. After the dry needling protocol, each subject completed a questionnaire regarding demographic information, individual lifestyle, and pretreatment pain function. The questions about individual lifestyle assessed factors such as smoking, drinking, sleep deprivation, and nutritional inadequacies. The questionnaire assessed whether the subjects had smoked 100 or more cigarettes in their lifetimes, whether they currently smoked cigarettes every day or some days, whether they consumed 10–45 g of alcohol per day, whether they subjectively needed sleep 1 h > actual sleep time, and whether they had ever been diagnosed with a vitamin or iron deficiency [2, 17].

The Taiwan version of the Brief Pain Inventory (BPI-T) was used [2, 18]. The BPI-T developed from the original BPI measures intensity of pain (sensory dimension) and interference of pain in daily life (reactive dimension) on a simple numeric scale from 0 to 10. Pain intensity was assessed by a four-item self-reported inventory requiring patients to rate their pain at the time of completing the questionnaire (present pain) and also when it was "worst," "least," and "average" within the previous week. Due to no significant improvement in BPI least pain score between baseline and 1 year postoperatively, the present study finally did not predict least pain in multiple linear regression models after dry

needling. Pain severity was measured on a scale from 0 (no pain) to 10 (extreme pain). A similar seven-item self-reported inventory was used to measure interference of pain with daily life, including general activity, mood, walking ability, normal work, relationships with others, sleep, and enjoyment of life. The anchor points for each of the interference scale items were "0" ("no interference") and "10" ("extreme interference"). In addition to reporting present pain intensity, patients were instructed to indicate any changes in the type of pain and any use of nonpharmacological pain treatment. The coefficient alpha regarding internal reliability was 0.84 for the severity scale and 0.88 for the interference scale.

All data collection was performed by the trained research assistant. Baseline data collection was as follows: pain questionnaire and BPI-T (both at pain clinic); follow-up BPI-T by telephone interview one year later.

2.4. System Model Development. The factors used in the MLR model to predict 1-year pain function of dry needling patients included patient characteristics. The MLR model can be formulated as the following linear equation:

$$\widehat{Y} = \beta_0 + \beta_i X_i + \varepsilon_i, \quad i = 1, 2, \ldots, m, \tag{1}$$

where $\widehat{Y}$ is the actual output value, β_0 is the intercept, β_i is the model coefficient parameter, X_i is the independent or input variable, ε_i is the random error, and m is the number of variables.

The SVM model employs nonlinear mapping to transform the original training data into higher-dimensional data and searches for the linear optima that define a hyperplane within the new dimension [8]. With appropriate nonlinear mapping to a sufficiently high dimension, a decision boundary can separate data into two classes [8]. In the SVM model, this decision boundary is defined by support vectors and margins.

The ANN model used in this study was a standard feedforward, backpropagation neural network with three layers: an input layer, a hidden layer, and an output layer. The MLP network is an emerging tool for designing special classes of layered feedforward networks [19]. Its input layer consists of source nodes, and its output layer consists of neurons; these layers connect the network to the outside world. In addition to these two layers, the MLP usually has one or more layers of neurons referred to as hidden neurons because they are not directly accessible. The hidden neurons extract important features contained in the input data.

2.5. Statistical Analysis. The dataset was divided randomly into two sets, one set of 320 cases (80% of the overall dataset) for training the model and another set of eighty cases for testing the model. The model was built using the training set. Demographic and clinical characteristics were the independent variables, and the pain function was the dependent variable. The SVM, MLR, and ANN models were then tested using the eighty cases in the testing dataset.

The model fit and prediction accuracy of the system models were measured in terms of mean square error (MSE) and mean absolute percentage error (MAPE), respectively. The MSE, which is computed between the desired and predicted values and then averaged across all data, is used as an indicator of goodness of fit. The MAPE indicates the average deviation from the desired value and is usually expressed as a percentage [9, 19]. The prediction accuracy of a model is considered excellent if its MAPE value is lower than 10%. Values between 10% and 20%, between 20% and 50%, and higher than 50% are considered indicators of high, average, and low prediction accuracy, respectively [9, 19]. The formulas for calculating MSE and MAPE are

$$\begin{aligned} \text{MSE} &= \frac{1}{n}\sum_{i=1}^{n}\left(Y_i - \widehat{Y}_i\right)^2, \\ \text{MAPE} &= \frac{1}{n}\sum_{i=1}^{n}\frac{\left|Y_i - \widehat{Y}_i\right|}{Y_i} \times 100\%, \end{aligned} \tag{2}$$

where n is the number of observations, Y_i is the desired (target) value of the ith observation, and $\widehat{Y}_i$ is the actual output value of the ith observation.

The change rates are also given. The optimal number of neurons in the hidden layer and the activation functions are iteratively determined by comparing the MSE index of the output error among several neural networks. The network training process continues as long as training and test errors decrease. That is, training stops when the training error rate and test error rate no longer change or when they begin increasing. The prediction accuracy of the model is then judged by computing the MAPE value. The change rate is also used to compare model performance between the training and test sets. This criterion is used to calculate the difference in MSE index between the test and the training sets so that the better model can be identified. Absolute value was defined as [(the MSE value from test set − the MSE value from training set)/(the MSE value from training set)] × 100%. The lower the change rate and the lower the MSE value are, the better the model performs.

The unit of analysis in this study was the individual MPS patients after dry needling. The data analysis was performed in several stages. Firstly, continuous variables were tested for statistical significance by one-way analysis of variance (ANOVA), and categorical variables were tested by Fisher's exact analysis. Univariate analyses were applied to identify significant predictors ($P < 0.05$). Secondly, STATISTICA 10.0 (StatSoft, Tulsa, OK, USA) software was used to construct the MLP network model, the SVM model, and the MLR model of the relationship between the identified predictors and pain function. Finally, to simplify the training process, key variables were introduced, and unnecessary variables were excluded. A global sensitivity analysis was also performed to assess the relative significance of input parameters in the system model and to rank the variables in order of importance. The global sensitivity of the input variables against the output variable was expressed as the ratio of the network error (variable sensitivity ratios, VSR) with a given input omitted to the network error with the input included. A ratio of 1 or lower indicates that the variable degrades network performance and should be removed.

Table 1: Patient characteristics of analyzed subjects ($N = 400$).

Variables	N (%) or means ± SD
Age, years	48.57 ± 12.63
Pain duration, months	42.53 ± 40.21
Gender	
Female	283 (71.0%)
Male	117 (29.0%)
Marital status	
Single	96 (23.9%)
Married	304 (76.1%)
Education	
No formal education/primary school	100 (25.0%)
Junior high school	152 (38.0%)
Senior high school/college	148 (37.0%)
Drinking	
Yes	41 (10.3%)
No	359 (89.7%)
Smoking	
Yes	35 (8.8%)
No	365 (91.2%)
Sleep deprivation	
Yes	116 (29.0%)
No	284 (71%)
Nutritional deficiency	
Yes	27 (6.8%)
No	373 (93.2%)
Pretreatment pain intensity: worst, score	5.97 ± 1.72
Pretreatment pain intensity: least, score	2.18 ± 1.83
Pretreatment pain intensity: average, score	4.41 ± 1.67
Pretreatment pain intensity: present, score	4.11 ± 3.47
Pretreatment aggregated pain interference, score[#]	3.15 ± 2.03

SD: standard deviations.
[#]Aggregated pain interference was calculated as follows: [(pain interference of general activity + mood + walking ability + normal work + relationship + sleep + enjoyment of life)/7] .

3. Results

Table 1 shows the patient's characteristics in this study. The mean age of the study population was 48.57 years (standard deviation, SD = 12.63 years). The average pain duration was 42.53 months (SD = 40.21 months), and 71.0% of the patients were female. Table 2 shows the coefficients for worst pain, average pain, present pain, and aggregated pain interference obtained by the training set in the MLR model. The selected variables included in the MLR models were age, pain duration, gender, marital status, sleep deprivation, nutritional deficiency, and pretreatment BPI score. All the selected variables were statistically significant ($P < 0.05$).

Table 3 shows the three-layer networks and number of support vectors of worst pain, average pain, present pain, and aggregated pain interference in ANN and SVM models. The ANN-based approaches provided the 3-layer networks and the relative weights of neurons used for predicting BPI score. The activation functions of logistic sigmoid and hyperbolic tangent were used in each neuron of the hidden layer and output layer, respectively.

Table 4 compares the BPI score predictions obtained by the ANN, the SVM, and the MLR models for the training set and the test set. For predicting BPI score, the ANN model had relatively larger change rates of MSE values at year 1. That is, the ANN model had better BPI score prediction capability. Apparently, the ANN model also outperformed the SVM model and the MLR model in terms of predictive accuracy. Most MAPE values obtained by the ANN model were lower than 5%, which indicated the excellent accuracy of the ANN in predicting BPI score.

The training set was also used to calculate the variable sensitivity ratios (VSR) for the ANN model. Table 5 presents the VSR values for the outcome variables (BPI scores) in relation to the four most influential variables. In the ANN model, pretreatment BPI score was the most influential (sensitive) parameter in terms of its effects on worst pain, average pain, present pain, and aggregated pain interference (VSR 5.83, 5.51, 5.15, and 6.07, resp.). All VSR values exceeded one, indicating that the network performs better when all variables are considered.

Table 6 compares the MAPE values obtained by ANN and SVM models. Compared to the SVM model, the ANN model consistently obtained lower MAPE values for worst pain score (4.7% versus 6.0%), average pain (4.4% versus 5.8%), present pain (4.1% versus 5.4%), and aggregated pain interference (3.6% versus 4.8%).

4. Discussion

This study confirmed that, compared to the SVM model and the MLR model, the ANN model is significantly more accurate in predicting pain function ($P < 0.001$). To the best of our knowledge, this study is the first to use ANNs for analyzing predictors of BPI score after dry needling. This model was tested against actual outcomes obtained by a neural network model, a support vector machine model, and a linear regression model constructed using identical inputs. We also showed that, given the same number of demographic and clinical inputs and pretreatment BPI scores, the predictive accuracy of ANN is superior to that of SVM and MLR.

Recently, SVM and ANN models have been used for nonlinear modeling in many fields, particularly bioinformatics [6–10]. Although the efficacy of SVM models is well established in the field of machine learning, its performance in surgical outcome prediction and prognosis has not been measured. The ANNs are adaptive models that use a dynamic approach to analyzing the risk of outcomes. That is, they perform bottom-up computation by modifying their internal structures in relation to a functional objective (i.e., the model is generated by the data it analyzes). Despite their incapability to deal with missing data, ANNs can simultaneously process numerous variables and can consider outliers and nonlinear interactions among variables. Unlike standard statistical tests,

Table 2: Coefficients of significant variables for Brief Pain Inventory (BPI) scores in multiple linear regression model after dry needling.

Variables	Worst pain		Average pain		Present pain		Aggregated pain interference*	
	Coefficients	*P* value	Coefficients	*P* value	Coefficients	*P* value	Coefficients	*P* value
Age	−0.03	0.041	−0.04	0.045	−0.03	0.044	−0.05	0.029
Pain duration	0.28	<0.001	0.01	0.021	0.03	0.037	0.01	0.035
Gender (female versus male)	−0.51	0.036	−0.64	0.023	−0.69	0.031	−0.71	0.030
Marital status (single versus married)	0.54	0.039	0.67	0.014	0.68	0.014	0.59	0.038
Sleep deprivation (yes versus no)	1.53	<0.001	1.14	<0.001	0.98	0.012	1.06	<0.001
Nutritional deficiency (yes versus no)	1.82	<0.001	1.60	0.018	1.90	<0.001	1.71	0.001
Pretreatment BPI score	0.58	<0.001	0.34	<0.001	0.46	<0.001	0.28	<0.001

*Aggregated pain interference was calculated as follows: [(pain interference of general activity + mood + walking ability + normal work + relationship + sleep + enjoyment of life)/7].

Table 3: Three-layer networks and number of support vectors for Brief Pain Inventory (BPI) scores in artificial neural network (ANN) and support vector machine (SVM) models.

Subscales	ANN-based model*	SVM-based model#
Worst pain	11-5-1	143
Average pain	11-7-1	93
Present pain	11-5-1	119
Aggregated pain interference	11-4-1	127

*Values are for input layer-hidden layer-output layer.
#Values are numbers of support vectors.

ANNs effectively manage complexity even when samples sizes are small and when ratios between variables and records are unbalanced. In this respect, ANNs avoid the dimensionality problem and can achieve a predictive accuracy superior to those of SVM and MLR. To ensure a sufficiently robust basis for network training, the present study used a large and homogeneous dataset comprising all demographic and clinical variables shown to affect patient-reported BPI scores in previous linear regression models [9].

Throughout this one-year follow-up study, the best single predictor of BPI scores was pretreatment pain function, which is consistent with reports that pretreatment functional scores are the best predictors of posttreatment QOL [2, 9]. Therefore, effective counseling is essential for apprising patients of expected posttreatment impairments. If QOL outcomes are considered benchmarks, then pretreatment functional status, which is a major predictor of posttreatment outcome, is crucial. Patients should also be advised that their posttreatment QOL might depend not only on the success of their treatments, but also on their pretreatment functional status.

To identify prognostic indicators after dry-needling protocol, prospective cohort follow-up studies are essential for identifying prognostic predictors. The results of the authors' analyses also showed the importance of baseline pain intensity in predicting outcomes. In agreement with previous studies, baseline pain intensity was powerful outcome predictor of musculoskeletal pain across different regional pain sites [2, 20]. More pain predicted a lower probability of recovery

Table 4: Comparison of multiple linear regression (MLR), support vector machine (SVM), and artificial neural network (ANN) models in predicting Brief Pain Inventory (BPI) scores.

Indices	Models	Training set (*A*)	Testing set (*B*)	Change rate#
Worst pain				
MSE	MLR	22.41	24.37	8.7%
	SVM	16.05	14.52	10.5%
	ANN	15.02	12.63	20.3%
MAPE	MLR	8.5%	8.1%	—
	SVM	5.9%	5.1%	—
	ANN	4.4%	4.5%	—
Average pain				
MSE	MLR	19.19	17.84	7.6%
	SVM	13.93	12.86	8.3%
	ANN	13.26	11.56	14.7%
MAPE	MLR	6.4%	6.2%	—
	SVM	5.5%	5.9%	—
	ANN	4.0%	4.1%	—
Present pain				
MSE	MLR	17.68	18.82	6.1%
	SVM	12.06	13.01	7.3%
	ANN	10.31	11.16	7.6%
MAPE	MLR	6.9%	6.9%	—
	SVM	5.7%	5.0%	—
	ANN	4.6%	4.4%	—
Aggregated pain interference				
MSE	MLR	14.83	14.28	3.9%
	SVM	11.06	10.18	8.6%
	ANN	8.13	8.91	8.8%
MAPE	MLR	5.6%	5.4%	—
	SVM	4.5%	4.7%	—
	ANN	3.4%	3.4%	—

MSE: mean square error, MAPE: mean absolute percentage error.
#Change rate = $|(B - A)/(A)| \times 100\%$.

Table 5: Global sensitivity analysis of artificial neural network (ANN) model in predicting Brief Pain Inventory (BPI) scores.

ANN model	Rank 1st VSR	Rank 2nd VSR	Rank 3rd VSR	Rank 4th VSR
Worst pain	Pretreatment worst pain score (5.83)	Sleep deprivation (1.74)	Pain duration (1.43)	Nutritional deficiency (1.24)
Average pain	Pretreatment average pain score (5.51)	Sleep deprivation (1.66)	Pain duration (1.52)	Nutritional deficiency (1.44)
Present pain	Pretreatment present pain score (5.15)	Sleep deprivation (1.60)	Pain duration (1.20)	Nutritional deficiency (1.18)
Aggregated pain interference	Pretreatment aggregated pain interference score (6.07)	Pain duration (1.57)	Sleep deprivation (1.44)	Nutritional deficiency (1.30)

VSR: Variable sensitivity ratios.

Table 6: Comparison of mean absolute percentage error (MAPE) in Brief Pain Inventory (BPI) scores predicted by multiple linear regression (MLR), support vector machine (SVM) and artificial neural network (ANN) models in forty new data sets.

Models	MAPE
Worst pain	
MLR model	8.2%
SVM model	6.0%
ANN model	4.7%
Average pain	
MLR model	6.7%
SVM model	5.8%
ANN model	4.4%
Present pain	
MLR model	6.8%
SVM model	5.4%
ANN model	4.1%
Aggregated pain interference	
MLR model	5.7%
SVM model	4.8%
ANN model	3.6%

at followup. Having more pain and disability at baseline will leave room for a larger reduction at follow-up. Although, this does not necessarily result in a better prognosis in terms of recovery, the pain intensity may still be relatively high at followup. For example, a patient with a baseline pain score of 9 and a follow-up score of 5 improved more than a patient with a baseline score of 4 and a follow-up score of 1 [21].

Sleep deprivation does produce hyperalgesic changes in healthy subjects [22], which likely reflect alterations in supraspinal modulation of nociception such as impaired function of inhibitory modulation pathways. Sleep deprivation has a much larger effect on muscle nociception than on skin nociception [23]. Furthermore, sleep deprivation is known to produce additional effects such as increased fatigue and negative mood, which might cause a modulation of pain processing. Depression, which is strongly associated with poor mental QOL, is only moderately associated with poor physical QOL [24, 25]. However, sleep problems are apparently related to poor physical QOL [24, 25]. In the present study, sleep deprivation was significantly and positively related to BPI scores.

Longer pain duration at baseline was indicative of poor prognosis for spinal pain, low back pain, shoulder pain, and hip pain [26]. ANN model was used to predict BPI scores, and this study results showed that pain duration was secondary rank factor for aggregated pain interference. Atroshi et al., using the SF-36 to investigate long-term sick leave among primary care patients with musculoskeletal disorders, found the long-term sick listed patients had significantly worse physical and mental health [27]. Among longer pain duration patients, physical functioning scores had not improved at one year despite a small to moderate improvement in pain scores.

The ANN approach developed in this study extends the predictive range of the linear regression model by replacing identity functions with nonlinear activation functions. The approach is apparently superior to linear regression for describing systems. The ANNs may be trained with data acquired in various clinical contexts and can consider local expertise, racial differences, and other variables with uncertain effects on clinical outcomes. The analysis need not be limited to clinical parameters. Other potentially useful variables could be tested to improve the predictive value of the model. The proposed ANN architecture with MLP can also include more than one dependent variable and can perform a nonlinear transformation between dependent variables. Future studies may evaluate how other demographic or clinical characteristics affect the proposed architecture.

Although all research questions were satisfactorily addressed, several limitations are noted. This study collected data for myofascial pain control after dry needling under the supervision of two physicians in one medical center, each of whom had performed the highest volume of myofascial pain control after dry needling during the previous years. This sample selection procedure ensured that patient's outcome data would not be affected by physicians with limited experience. However, a notable limitation is that the first patient in the prospective patient cohort was enrolled in 2008. Therefore, depending on their inclusion date, some MPS patients had a longer followup than others did, which may have caused selection bias. Nonetheless, in most QOL subscales, the characteristics of subjects who continuously

participated throughout this one-year study did not significantly differ from those of subjects who died or dropped out during the study (data not shown).

5. Conclusions

Compared with the SVM model and the MLR model, the ANN model in the study was more accurate in predicting patient-reported QOL and had higher overall performance indices. The global sensitivity analysis also showed that pretreatment pain function is the most important predictor of BPI scores after dry needling. The predictors analyzed in this study could be addressed in pretreatment and posttreatment health care consultations to educate candidates for MPS patients dry needling in the expected course of recovery and expected functional outcomes. Further studies of this model may consider the effect of a more detailed database that includes complications and clinical examination findings as well as more detailed outcome data. Hopefully, the model will evolve into an effective adjunctive clinical decision making tool.

Conflict of Interests

The authors have no personal, professional, or financial conflict of interests to declare.

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Research Article

Remote Effect of Lower Limb Acupuncture on Latent Myofascial Trigger Point of Upper Trapezius Muscle: A Pilot Study

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Objectives. To demonstrate the use of acupuncture in the lower limbs to treat myofascial pain of the upper trapezius muscles via a remote effect. *Methods*. Five adults with latent myofascial trigger points (MTrPs) of bilateral upper trapezius muscles received acupuncture at Weizhong (UB40) and Yanglingquan (GB34) points in the lower limbs. Modified acupuncture was applied at these points on a randomly selected ipsilateral lower limb (experimental side) versus sham needling on the contralateral lower limb (control side) in each subject. Each subject received two treatments within a one-week interval. To evaluate the remote effect of acupuncture, the range of motion (ROM) upon bending the contralateral side of the cervical spine was assessed before and after each treatment. *Results*. There was significant improvement in cervical ROM after the second treatment ($P = 0.03$) in the experimental group, and the increased ROM on the modified acupuncture side was greater compared to the sham needling side ($P = 0.036$). *Conclusions*. A remote effect of acupuncture was demonstrated in this pilot study. Using modified acupuncture needling at remote acupuncture points in the ipsilateral lower limb, our treatments released tightness due to latent MTrPs of the upper trapezius muscle.

1. Introduction

Acupuncture is commonly used in traditional Chinese medicine for relief of myofascial pain syndrome [1]. The efficacy of acupuncture depends on various factors, including the site of needling, the intensity of acupuncture, and the mode of needle stimulation. The needling can be placed at either local or distant acupuncture points, and several studies have reported effective pain relief [2–4]. When acupuncture has an effect on a location far from the site of needle insertion (usually along the same channel), it is called a "remote effect" [3].

The "intensity of acupuncture" is related to factors including the number of sites needled per session, number and frequency of sessions, and depth of needle insertion. The mode of stimulation depends upon the method of manipulation, which includes needle twisting and additional electrical stimulation (electroacupuncture). However, the various options regarding intensity of acupuncture have not yet been standardized.

The remote effect of acupuncture in patients with active myofascial trigger points (MTrPs) has recently been reported [5–7]. However, the remote effect of acupuncture on upper body MTrPs from lower limbs has not been investigated.

MTrPs are considered as localized hyperirritable spots in palpable taut bands of skeletal muscle fibers [8–22]. The characteristics of an MTrP [8, 9, 13, 14, 16–24] include the following: (1) a discriminate tender spot in a palpable taut band; (2) a consistent and characteristic referred pain pattern upon compression of an MTrP; (3) a local twitch response elicited by snapping palpation on MTrPs in some muscles or

by needling of MTrPs in almost all cases; (4) restricted range of stretch (or motion of the involved joint); and (5) associated referred autonomic phenomena including vasoconstriction, coldness, sweating, pilomotor response, ptosis, and/or hypersecretion. MTrPs can be classified as active or latent [15, 17, 18]. An active MTrP is characterized by spontaneous pain or pain in response to movement, while a latent MTrP is a sensitive spot with pain or discomfort in response to compression, only. In other words, patients with latent MTrPs may only have functional changes, such as limitation of range of motion (ROM), but no painful sensation combined with the functional change. It has been suggested that the treatment of latent MTrPs in patients with musculoskeletal pain may not only decrease pain sensitivity and improve the motor function, but it also prevent their transformation into active MTrPs, thereby preventing the development of myofascial pain syndrome [25]. Coincidentally, increasing numbers of studies have shown that some MTrPs are actually the acupuncture points, the so-called "Ah-Shi" points [26–29].

The aim of this study was to investigate the remote effect of modified acupuncture in the lower limbs of adults with latent MTrPs of their upper trapezius muscles. We hypothesized that modified acupuncture could suppress the irritability of latent MTrPs of the upper trapezius muscle after remote acupuncture in the ipsilateral lower limb, which would lead to the improvement in cervical ROM.

2. Methods

2.1. General Design. This study was approved by our Institutional Review Board, and all subjects gave their written informed consent prior to participation in the study.

Five adults with latent MTrPs of bilateral upper trapezius muscles received modified acupuncture therapy applied on a randomly selected ipsilateral lower limb (experimental side) versus sham needling on the contralateral lower limb (control side) in each subject. The acupuncture points in the ipsilateral lower limb selected for acupuncture therapy were Weizhong (BL40, on the posterior aspect of the knee, at the midpoint of the popliteal crease) and Yanglingquan (GB34, on the fibular aspect of the leg, in the depression anterior and distal to the head of the fibula) [30]. Each subject received one treatment on both lower limbs weekly for a total of 2 weeks. The ROM upon bending the contralateral side of the cervical spine was assessed before and after each treatment to evaluate for any remote effect. Pain intensity of the acupuncture site was also assessed using the visual analog scale (VAS) (Figure 1).

2.2. Subjects. All five adult subjects suffered from myofascial pain in their bilateral upper trapezius muscles for at least 3 months prior to enrollment in this study. Upon enrollment, pain over the upper trapezius muscle had diminished, but functional limitation in cervical ROM persisted. Besides, there was at least one latent MTrP of each upper trapezius muscle. The latent MTrPs were identified according to the following criteria: the presence of a sensitive, tender point in the palpable taut band within the upper trapezius muscles, pain induced only by external compression over the taut band with absence of spontaneous pain from this tender point. Exclusion criteria were coexisting pain in the lower back or any limb; contraindications for acupuncture such as bleeding tendency, local infection, severe medical illness, trauma, or pregnancy; history of drug or alcohol abuse which might interfere with the assessment of pain; a history of surgery on the neck, back, or any limb; a history of any neurologic disease involving either the central or peripheral nervous systems; cognitive deficits; and any history of prior acupuncture treatment.

A detailed explanation of the therapeutic and assessment procedure was given to each subject. All subjects were informed that they would receive one of two different acupuncture needling techniques for the relief of trapezius muscle tightness, but they were unaware as to which limb was chosen for the experimental side versus the control side. The decision regarding the choice of limb for the experimental acupuncture was determined by each subject who selected one of two envelopes containing either the letter "L" or "R". The letter "L" indicated that the subject would receive modified acupuncture therapy on the left lower limb and "R" indicated the receipt of modified acupuncture therapy on the right lower limb.

2.3. Acupuncture Procedure. Each subject received acupuncture at both Weizhong (BL40) and Yanglingquan (GB34) acupuncture points using the modified acupuncture method on the randomly selected experimental side (modified acupuncture group) and sham needling on the contralateral limb (control group). Each subject received the same treatment to both lower limbs one week later. Each acupuncture point was treated for 3 minutes with the subject in the prone position with legs straightened in order to achieve maximal relaxation of the entire body and to avoid syncope during needling. One-inch, no. 30 gauge, disposable acupuncture needles were used. A licensed acupuncturist, who was blinded to the assessment, performed the procedure.

In the modified acupuncture group, the acupuncture needle was inserted into the muscular layer at a regular depth. The needle was then moved in-and-out for a distance of between 5–15 mm below the skin level and twisted clockwise and counterclockwise in multiple directions rapidly, as described by Chou et al. [6, 7], similar to the procedure for MTrP injection described by Hong [31]. As many as possible local twitch responses were elicited during the needle manipulation for 15 seconds, and then the acupuncture needle was fixed in place for 3 minutes. The "De-Qi" sensation was frequently elicited during this manner of needle manipulation. This sensation includes soreness, numbness, heaviness, and distension around the needle insertion region [32]. In the sham needling group, the acupuncture needle was inserted into the skin to a depth of 2 mm, and the needle was held in a small brass cylinder (Figure 2). No needle manipulations, such as moving in-and-out or clockwise or counterclockwise rotations, were performed. No "De-Qi" sensation or local twitch response was induced.

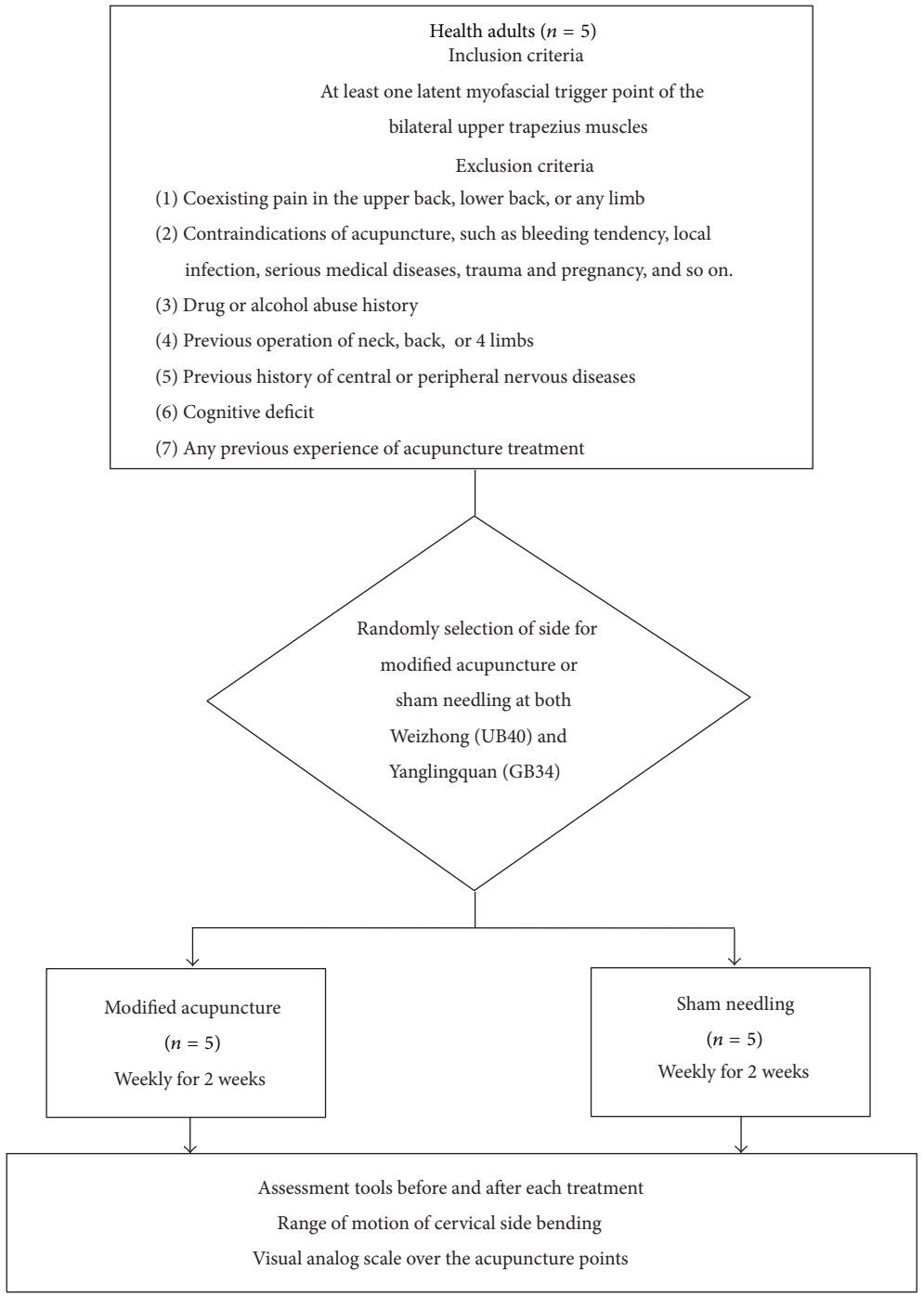

Figure 1: The flow diagram showing our study design.

2.4. Assessments. The effect of acupuncture was determined by measuring the ROM upon bending the contralateral side of the cervical spine compared to the opposite side before and after the 1st and 2nd treatments. The VAS was also recorded in order to assess any painful sensations at the acupuncture sites before, and immediately after, each acupuncture treatment. All the assessment procedures were performed by one of the authors who was blinded to the group assignment of the participants.

2.5. Cervical ROM. The ROM upon bending the contralateral side of the cervical spine was measured with a large-scale goniometer to determine the degree of tightness of the upper trapezius muscles. During each measurement, the patient was instructed to sit on an adjustable chair with each hand placed on the front of each thigh. The height of the chair could be adjusted to keep the spinous process of the C7 vertebra at the same horizontal level as the center of the large-scale goniometer. The subject was then asked to bend his

Figure 2: A small brass cylinder holds the acupuncture needle on the control side.

or her neck maximally to the right or left side for the least 5 seconds without any movement of the shoulders. Three consecutive measurements on each side were performed, and the average value was used for statistical analysis. If there was compensatory movement of shoulder and trunk during the measurement, the subject's position was rechecked, and he/she was given instructions on how to perform the measurement correctly.

2.6. VAS. As the participants with latent MTrPs had no pain at rest, the VAS was used only to monitor for any painful sensation at acupuncture site. The VAS score was recorded before, and immediately after, each acupuncture treatment. A card with an uncalibrated scale ranging from zero to ten on one side (with zero representing no pain and ten representing the worst imaginable pain) was shown to each participant. There was a corresponding 100 mm scale on the other side of the card. The participants subjectively estimated their pain level by moving the pointing device along the uncalibrated scale between zero and ten. The exact value of pain intensity was also read and recorded from the other side.

2.7. Statistical Analysis. The data from all measurements were collected before and after the 1st and 2nd acupuncture treatments. The degree of change in the values after the first treatment and before and after the second treatment was calculated using the following formula:

$$\text{Degree of change (\%)} = 100\% \times \frac{(\text{post-treatment value-pre-1st treatment value})}{(\text{pre-1st treatment value})} \quad (1)$$

A repeated-measures analysis of variance was used to compare the values before and after each treatment in each group. A paired t-test was used to compare the values between the modified acupuncture group and the sham needling group. $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences Version 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

Five healthy adults (3 men, 2 women) with latent MTrPs of both upper trapezius muscles were recruited. Their ages ranged from 29 to 40 years with a mean age of 32.8 ± 5.3 years. All outcome assessments were expressed as mean ± standard deviation, as shown in Table 1.

Before the first acupuncture treatment, the ROM upon bending the contralateral side of the cervical spine measured 31.0 ± 7.7 degrees in the modified acupuncture group and 35.7 ± 8.9 degrees in the sham needling group. Because there was a significant difference in ROM between the two groups, data normalization, that is, the "degree of change," was used for comparison. After the first modified acupuncture and sham treatment, there was no significant improvement in the ROM in either group ($P > 0.05$).

In the control group, there was no significant change in ROM after the second sham needling treatment ($P > 0.05$). In contrast, the ROM in the experimental group increased to 35.1 ± 9.0 degrees after the second modified acupuncture treatment. The degree of change was statistically significant, compared to the value before the second treatment ($P = 0.030$). The increased ROM on the modified acupuncture side was greater compared to the sham needling side ($P = 0.036$).

Because all participants in this study were adults with latent rather than active MTrP, the baseline VAS score for all subjects was zero. After the first acupuncture treatment, there was a transient increase in VAS score (0 versus 0.5 ± 0.3, $P = 0.023$) at the acupuncture site, which completely subsided before the second acupuncture treatment. There was no significant difference in VAS scores before and after the second acupuncture treatment (0 versus 0.7 ± 0.9, $P = 0.171$).

4. Discussion

In this study, participants with latent MTrPs were selected for the evaluation of a remote acupuncture effect using a modified technique. This remote effect was assessed by the degree of tightness of the upper trapezius muscle containing MTrP as determined by the degree of change in cervical ROM. We found that distal acupuncture, using a method similar to that used for myofascial pain injection, could relieve proximal muscular tightness and lead to an increase in cervical ROM. As our subjects with latent MTrP did not suffer from pain at baseline, the change in VAS score was measured over the acupuncture site only to ascertain whether any pain was induced by the acupuncture, itself. We found that transient pain developed only after the first acupuncture treatment, and, thus, adaptation to the pain after the first acupuncture occurred.

4.1. The Local and Remote Effects of Acupuncture. In previous reports in the literature, either local or distant acupuncture points were selected for pain relief in patients with myofascial pain. Ceccherelli et al. recruited patients with cervical myofascial pain [33]. The acupuncture points around the

Table 1: The range of motion upon bending the contralateral side of the cervical spine in two groups before and immediately after acupuncture treatments.

Group	Before the 1st treatment	After the 1st treatment		Before the 2nd treatment		After the 2nd treatment		P value[†]			
	Pre-1st (degree)	Post-1st (degree)	DOC[*] (%)	Pre-2nd (degree)	DOC[*] (%)	Post-2nd (degree)	DOC[*] (%)	Pre-1st versus Post-1st	Pre-1st versus Pre-2nd	Pre-1st versus Post-2nd	Pre-2nd versus Post-2nd
Modified acupuncture	31.0 ± 7.7	32.8 ± 10.4	4.5 ± 10.6	30.1 ± 7.5	−1.9 ± 14.7	35.1 ± 9.0	14.7 ± 17.2	0.308	0.727	0.170	0.030[§]
Sham needling	35.7 ± 8.9	34.9 ± 3.8	1.1 ± 18.8	33.4 ± 7.2	−3.4 ± 24.5	34.6 ± 8.0	−1.6 ± 17.1	0.777	0.588	0.714	0.452
P value[‡]	0.021[§]		0.784		0.870		0.036[§]				

Pre-1st: the value before the first treatment; post-1st: the value after the first treatment; pre-2nd: the value before the second treatment; post-2nd: the value after the second treatment; and DOC: degree of change. Values are mean ± standard deviation or P value.

[*] Degree of change was calculated by 100% × (post-treatment value − pre-1st treatment value)/(pre-1st treatment value).

[†] Repeated measured ANOVA was used to compare the values within the same group.

[‡] Paired t-test was used to compare the values between two groups.

[§] $P < 0.05$.

neck and shoulder girdle (such as Tianzhu (BL10), Fengchi (GB20), Dazhui (GV14), and Yamen (GV15)) and in the upper limbs (including Houxi (SI3), Waiguan (TH5), and Hegu (LI4)) were selected for eight sessions of stimulation. The authors found that the pain intensity evaluated by the McGill Pain Questionnaire was reduced at the end of treatment, and was sustained at 1 and 3 months later. This study supported the hypothesis that the cervical myofascial pain could be relieved by acupuncture at both local and distal acupuncture points. In the study by Irnich et al., a positive effect of distant acupuncture was also demonstrated [34]. Thirty-six patients with chronic myofascial neck pain were randomly assigned to receive one session of acupuncture at distant acupuncture points, dry needling in the MTrP of the neck and shoulder girdles, or sham laser at distant acupuncture points. Measurements of motion-related pain by VAS, cervical ROM in six directions, and change in verbal rating score were performed immediately after treatment. The selected acupuncture points were distributed in the posterior neck (GV20, GV14), trunk (KI 27, CV21, and CV22), upper limb (LU7, LI4), lower limbs (SI3, BL60), and ears (cervical spine, stellate ganglion). They found that the group with distant acupuncture treatment had lower scores by VAS, greater improvement in cervical ROM, and a greater decrease in verbal rating scores ($P < 0.05$ for all assessments). In a recent study by Chou et al. [6], distant acupuncture points in the upper limbs (TE5, LI11) were selected for the treatment of active MTrPs of the upper trapezius muscles. They also demonstrated a significant decrease in pain intensity and endplate noise amplitude in the MTrP region of the upper trapezius muscle.

In our study, the two acupuncture points selected for treatment, Weizhong (BL40) and Yanglingquan (GB34), were based on the traditional theory of "meridian" [35]. We found that modified acupuncture at these two acupuncture points in the lower limbs was effective in increasing cervical ROM. In the clinical practice in our country [35], Yanglingquan (GB34) is the principal acupoint for pain relief for myofascial pain syndrome. According to traditional theory, it is one of the eight meeting points where the "qi" of the tendon gathers. The tendon in classical literature indicates soft tissue (such as muscle, tendon, and fascia) in modern medicine. Weizhong (BL40) is the commonly recommended distant acupuncture point to relieve back pain [35].

4.2. The Issue of Acupuncture Application. The proper method of manipulation of the acupuncture needle is a key factor in achieving a positive effect from acupuncture. Ceccherelli et al. compared the effects of superficial acupuncture with those of deep acupuncture at both acupuncture points and trigger points in patients with lumbar myofascial pain [36]. In the superficial acupuncture group, the needle was introduced into the skin to a depth of 2 mm, whereas in the deep acupuncture group, the needle was inserted into the muscular layer to a depth of 1.5 cm into either the muscle or the trigger points. The same needle stimulation was performed in both groups (stimulation for 1 minute after insertion and for 20 seconds every 5 minutes at 5, 10, and 15 minutes); the frequency of alternative right and left rotations of the needles was 2 Hz. They found that the intensity of pain was reduced in both groups immediately after 8 sessions of treatments, but deep acupuncture was significantly more effective than superficial acupuncture therapy 3 months after the treatments. In that study, they concluded that superficial acupuncture was not really a "sham" therapy but a less effective type of acupuncture. This finding supports the effectiveness of superficial dry needling therapy [37–39]. In our study, we used superficial needling into the skin (2 mm in depth) in the control group. No movement (in-and-out) or clockwise-counterclockwise manipulation was performed. No "De-Qi" sensation or local twitch response was induced. The acupuncture needle remained fixed in place for 3 minutes. A painful sensation was only noticed when the acupuncture needle was inserted into the skin. No change in cervical ROM was observed after this treatment in our study.

In a case reported by Chou et al. [5], acupuncture manipulation (similar to Hong's technique for MTrP injection) at distant acupuncture points was found to relieve proximal myofascial neck pain in a patient with fibromyalgia. The distant acupuncture points used by Chou et al. included acupuncture points in the back (SI11), upper limbs (GB21, TE14), and lower limbs (GB34, SP6). They later found that a remote influence exerted by the same needle manipulation at acupuncture points in the upper limb (Wai-huan, Qu-chi) was also effective for patients with active MTrP in the upper trapezius muscle [6]. In our study, we obtained similar findings by twisting the needle clockwise and counterclockwise alternatively during multiple insertions of the acupuncture needle (Chou's method) on distant acupuncture points in the lower limb and obtained similar findings. It is important to emphasize that both the "De-Qi" sensation and local twitch response were induced during needle manipulation in order to obtain a good result. Cervical ROM was improved after only two treatment sessions. Thus, the method of needle manipulation (and not the depth of needle) for eliciting local twitch response was the key factor in achieving a positive effect of acupuncture in our study. In addition, we selected the same acupuncture points (rather than a nonacupuncture point) for needling in the experimental versus control groups. As all points selected for needling were acupuncture points, we cannot exclude an "add-on" effect at the acupuncture points in this study.

4.3. The Method of Placebo Acupuncture. Several methods have been suggested for placebo acupuncture, including (1) sham acupuncture, (2) minimal acupuncture, (3) mock acupuncture, and (4) mock transcutaneous electrical nerve stimulation (TENS) [40]. Sham acupuncture has been described as insertion of the needle at some distance away from the acupuncture point with the same method of manipulation and stimulation as that inserted at the acupuncture point. It is the most commonly used placebo method. However, recent studies have shown that analgesic effects may also be produced through the activation of diffuse noxious inhibitory control [41]. Minimal acupuncture is performed by positioning the needles outside the acupuncture point and inserting the needles very superficially (1-2 mm) without any manipulation. This procedure can minimize the acupuncture

effect. However, this very light stimulation may produce pain relief in some patients who are very responsive to acupuncture stimulation (called "strong responders"). Mock acupuncture is performed with a small brass cylinder with a blind end, which is fixed to the patients' skin with plaster. The needle is inserted inside this cylinder but the tip of needle does not contact the skin. The lack of needling sensation is explained to the patient as the result of superficial anesthesia. Similar to mock acupuncture, mock TENS is performed by placing the TENS electrodes on the target skin with only light or sounds emitted from the machine but with the current output switched off. The lack of stimulation is explained as "subliminal stimulation" to the patient. In our present study, the method of acupuncture in the control group was somewhat similar to the minimal and mock acupuncture methods. A small brass cylinder with two open ends was held by the acupuncturist on participant's skin. The length of the cylinder was just 2 mm shorter than the length of the acupuncture needle. Thus, we ensured that the depth of the acupuncture needle was only 2 mm below the skin, and, therefore, minimal acupuncture was given. No positive remote effects were found when this method was used in our control group. In addition, we selected the same acupuncture points (rather than a nonacupuncture point) for needling in the experimental and control groups. This design minimized bias between the acupuncture points and nonacupuncture points and also minimized bias among different acupuncture points. The only differences between the experimental and control groups were the depth and the method of needling.

4.4. Current Theory of the Mechanism of the Acupuncture Effect. Diffuse noxious inhibitory control has been used to explain the efficacy of acupuncture [41]. The diffuse noxious inhibitory control model asserts that an analgesic effect can be obtained by noxious stimulation to any part of the body, and the magnitude of the analgesic effect is also related to the magnitude of the noxious stimulus. The other explanation for pain control of MTrPs by acupuncture is secondary to hyperstimulation analgesia [26]. According to this theory, pain can be relieved by hyperstimulation of the pain fibers produced by dry needling or acupuncture. The pathway of hyperstimulation analgesia is probably also via the diffuse noxious inhibitory control. The moderate-to-intense sensory input of hyperstimulation analgesia can be applied locally or at a distance from the painful site. Recent data also supports the hypothesis that analgesia provided by local acupuncture occurs through the activation of large afferent fibers, whereas analgesia induced by distant acupuncture is mediated by the excitation of small afferent fibers if the stimulation from the distant acupuncture is strong enough [2].

4.5. Study Limitations. Our study had several limitations including the small sample size (only five subjects were recruited) and low frequency of treatments (only two acupuncture treatments were given within a 1-week interval). Nevertheless, statistically significant improvement in cervical ROM was found in the experimental group compared to the controls. It is hoped that the results of this pilot study may stimulate further research on the effectiveness of remote acupuncture, in patients with active MTrPs in upper trapezius muscles.

5. Conclusion

We found that the distal acupuncture by a method similar to MTrP injection could relieve proximal muscular tightness and lead to improvement in cervical ROM in individuals with latent MTrP. We concluded that a remote effect on proximal latent MTrPs in the upper trapezius muscle was created by modified acupuncture at distant acupuncture points in the lower limb.

Conflict of Interests

We certify that no party having a direct interest and no any other commercial financial support in this study.

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Research Article

Neuromuscular Damage and Repair after Dry Needling in Mice

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Objective. Some dry needling treatments involve repetitive and rapid needle insertions into myofascial trigger points. This type of treatment causes muscle injury and can also damage nerve fibers. The aim of this study is to determine the injury caused by 15 repetitive punctures in the muscle and the intramuscular nerves in healthy mouse muscle and its ulterior regeneration. *Methods*. We repeatedly needled the *levator auris longus* muscle of mice, and then the muscles were processed with immunohistochemistry, methylene blue, and electron microscopy techniques. *Results*. Three hours after the dry needling procedure, the muscle fibers showed some signs of an inflammatory response, which progressed to greater intensity 24 hours after the procedure. Some inflammatory cells could still be seen when the muscle regeneration was almost complete seven days after the treatment. One day after the treatment, some changes in the distribution of receptors could be observed in the denervated postsynaptic component. Reinnervation was complete by the third day after the dry needling procedure. We also saw very fine axonal branches reinnervating all the postsynaptic components and some residual sprouts the same day. *Conclusion*. Repeated dry needling punctures in muscle do not perturb the different stages of muscle regeneration and reinnervation.

1. Introduction

Myofascial trigger points (MTrPs) are hyperirritable nodules within taut bands of skeletal muscle responsible for sensory, motor (stiffness, weakness, and restricted range of motion), and autonomic dysfunction [1].

Theories regarding the molecular pathophysiology of MTrPs suggest that they are the result of an abnormal depolarization of motor endplates [2]. These dysfunctional endplates translate the electrical potential to muscle contraction which creates localized sarcomere shortenings that give rise to the palpable nodule of an MTrP. After the nodule formation, a cascade of events leading to the local release of nociceptive substances occurs. Using a microdialysis needles, the following nociceptive and sensitizing substances have been detected: bradykinin, tumor necrosis factor-α (TNF-α), calcitonin gene-related peptide (CGRP), substance P (SP), interleukins (IL 1β, 6, 8, and 12), serotonin, and norepinephrine [3, 4]. These substances cause pain and perpetuate abnormal acetylcholine release [2].

One of the therapeutic techniques most commonly employed in the treatment of MTrPs is dry needling (DN) [5]. DN consists of the use of the mechanical stimuli of a needle to either eliminate or inactivate the MTrP. Some DN treatments may involve repetitive and fast needle insertions into the MTrP region [1] often obtaining therapeutic benefits [6]. Since the diameter of the needles commonly employed in this treatment ranges from 160 to 450 μm, in contrast to the 20 to 60 μm diameter of a normal adult myocyte, this type of intervention disrupts muscle fibers, motor endplates, and distal axons. This, in fact, is commonly considered to be one of the possible benefits of the technique, by destroying the dysfunctional motor endplates causing the MTrPs as well as the sarcomere shortening of myocytes related to them [1, 5]. Nevertheless, the effect of this neuromuscular injury on muscle fiber and nerve regeneration has not yet been adequately explored.

Muscle regeneration after minimal lesion was described many years ago [7, 8]. Firstly, there is an inflammatory

reaction that cleans the injured area of necrotic debris. Then, activated satellite cells proliferate and merge to create a myotube. Finally, myotubes synthesize actin and myosin myofilaments that assemble sarcomeres to be joined to those previously existing. Efficient muscle regeneration requires a small lesion area and good muscle irrigation [9]. The timing needed to develop the inflammatory reaction and the complete regeneration is already known. Most experimental minimal and mechanical injuries are regenerated within 7 to 10 days [7, 8]. Since neuromuscular synapses seem to be related to MTrP pathophysiology, we hypothesized that the DN can also damage the nerve fibers innervating them. The changes after denervation and factors favoring nervous reinnervation have been largely referred ([10]; see Bishop, 1982 [11], or Stirling and Stys, 2010 [12], for review).

A common initial question regarding DN is whether the laceration injury caused by repetitive insertions of the needle repairs by creating a scar in myofascial tissues or it results in "ad integrum" regeneration. No study to date has addressed this issue either for muscle, nerve, or neuromuscular junction, and this is the main objective of this study.

2. Materials and Methods

2.1. Animals. Experiments were performed on the *levator auris longus* (LAL) muscle of adult male Swiss mice (30 to 40 days postnatal; Criffa, Barcelona, Spain). This muscle was chosen because it is a subcutaneous and thin muscle with a well-known intramuscular nerve branching pattern and is easy to handle for histological techniques. Following the study, twenty-three mice were sacrificed by exsanguination under anesthesia. The mice were cared for in accordance with the guidelines of the European Community's Council Directive of 24 November 1986 (86/609/EEC) for the humane treatment of laboratory animals. This study was approved by the Ethics Committee of the Rovira i Virgili University.

2.2. Dry Needling. The animals were anesthetized with 2% tribromoethanol (0.15 mL /10 g body weight, I.P.), and then the treatment was performed (see Figure 1(a)(i)). Fifteen repeated punctures were performed on the muscle with the same type of acupuncture needle commonly used to treat MTrPs. Needles were 0.16 mm thick and 25 mm long. The muscle fiber diameter of rodents and men is similar (for the same level of activity). However, the needle for DN is proportionately greater for the LAL muscle (extremely flat and small, 2 cm^2) than most human muscles. For this reason, we employed the thinnest needle used for MTrP treatment and few punctures.

To minimize the number of animals sacrificed, both LAL muscles per mouse were used (see the two extracted LAL muscles in Figure 1(a)(ii)).

2.3. Samples. The first sample was obtained three hours after the treatment, and the remaining samples were obtained at one, three, five, and seven days after puncture (see Figure 1(b)). Both LAL muscles were extracted from each animal: the right LAL muscles were processed for immunohistochemistry techniques, and the left LAL muscles were processed for methylene blue staining. The samples processed for electron microscopy were either from the right or the left sides. Muscles were pinned on Silgard in small Petri dishes (see Figure 1(a)(ii)) and then fixed for histological techniques: (a) in 10% neutral formalin for 3 to 10 days for methylene blue; (b) in 4% paraformaldehyde in phosphate buffered saline (PBS, pH 7.4) for 45 minutes at room temperature (~22°C) for immunohistochemistry; (c) in 2 to 5% glutaraldehyde in 0.1 M cacodylate buffer for two hours for transmission electron microscopy.

2.4. Immunohistochemistry. Whole LAL muscles were removed and fixed in 4% paraformaldehyde in PBS (pH 7.4) for 45 minutes at room temperature (~22°C). The LALs were double labeled for axons with fluorescein isothiocyanate-(FITC-) conjugated antibodies against 200 kD neurofilament protein (Sigma; 1 : 500 in 1% BSA) and postsynaptic nicotinic acetylcholine receptors with tetramethyl rhodamine isothiocyanate (TRITC)-α-BTX. Muscles were mounted in Mowiol with p-phenylenediamine (Sigma).

2.5. Methylene Blue. The samples were exposed to a 1% methylene blue dissolved in 1% borax for two minutes. Subsequently, the samples were washed with distilled water for the three steps of two minutes each. Finally, we proceeded to dehydration and mounting with epoxy resin.

2.6. Electron Microscopy. Tissue samples from LAL muscles containing innervated areas were fixed in a glutaraldehyde (2%) solution for two hours and postfixed in 1% osmium tetroxide for two hours. After dehydration with increasing concentrations of ethanol and acetone, the tissue fragments were embedded in Spurr's resin (plastic) in transverse orientation. Sections 0.5–0.7 nm thick were cut with a Reichert Ultracut E microtome (Leica Microsystems, Bannockburn, IL, USA) and flattened on glass slides by heating on a hot plate. Some sections were stained with methylene blue and mounted with DPX for light microscopic examination.

Ultrathin sections stained with uranyl acetate and lead citrate were observed using a transmission electron microscope at 60 kV (JEOL 1011 Ltd., Tokyo, Japan). Cross-sections of neuromuscular junctions and intramuscular nerves were examined.

3. Results

3.1. Muscle Damage. After 15 repeated punctures in the LAL muscle, we analyzed structural changes at several time points. Muscular injuries were quite separated, and we could only observe a single muscle injury by field at low magnification (4x).

Three hours after treatment, we found that some punctures were so shallow that they did not reach sufficient depth to injure the muscle fibers and only the connective tissue was injured. The initial inflammatory response was present in the injured connective tissue (Figure 2(a)). As

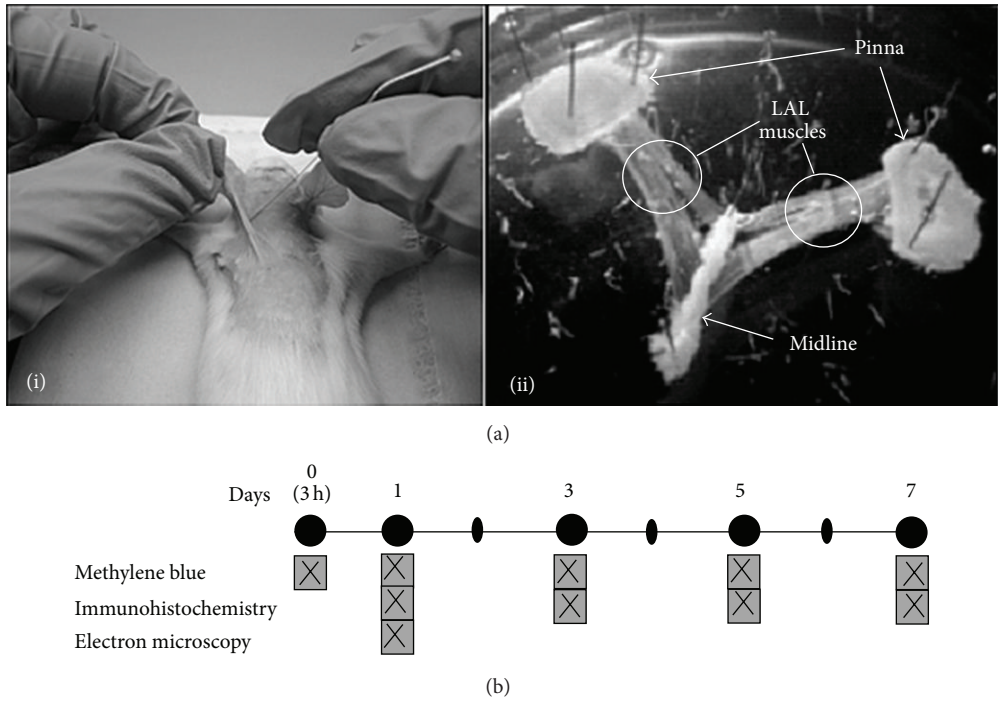


Figure 1: Experimental design and sampling. (a)(i) *Levator auris longus* (LAL) muscle in which repeated punctures are being made with a 0.16 mm thick needle. (a)(ii) Two LAL muscles obtained from the same mouse. (b) Techniques performed and experimental design. After DN, the animals were sacrificed on days one (three hours), two, three, five, and seven. After sacrifice, the muscles were removed, and histological techniques were performed as shown in the figure. In order to minimize the number of animals sacrificed and expenses, the days of extraction and the techniques used were chosen based on a preliminary pilot study.

expected, in deeper punctures the damage of muscle fibers was observed on day zero, three hours after intervention (Figure 2(b)). In this situation, the edges of the lesion began to trigger an inflammatory response. At 24 hours after the punctures, a complete inflammatory reaction of the damaged muscle fibers could be observed (Figure 2(c)). Three days after puncture, the muscles were in the initial phase of regeneration presenting an inflammatory reaction (Figure 2(d)). This cleans the necrotic debris of the injured area while preserving the healthy parts of the muscle fibers (compare Figures 3(a) and 3(b)).

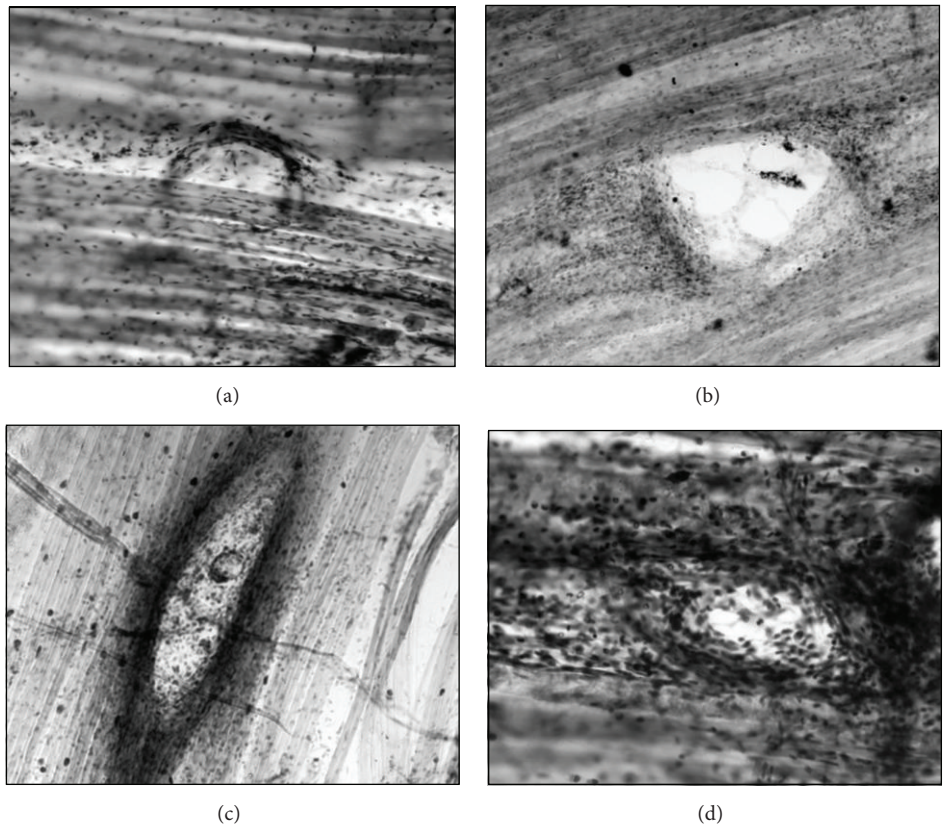
On the third day, satellite cells were activated and transformed into myoblasts. These myoblasts initiate a period of mitotic proliferation. The myoblasts are the first step of muscular regeneration. Figure 4 shows inflammatory reaction cells coexisting with myoblasts. The necrotic debris was completely phagocytized by the inflammatory reaction, and muscle fibers remained healthy at the lesion edges. Between days three and five after injury, the myoblasts fused with each other and with the healthy parts of the injured muscle fibers. The resulting cell of this fusion is the myotube (see Figure 5). Myotubes start the synthesis of actin and myosin (myofibrillogenesis; Figure 5(a)). At day five after injury, the myotubes were already in an advanced stage of myofibrillogenesis, and most of the cytoplasm appeared occupied by the neosynthesized contractile apparatus (Figure 5(a)). Not all myoblasts were fused, and the remaining ones became satellite cells that could be clearly identified by day five and day seven after the treatment (see Figures 5(a) and 5(b)). As observed in humans, mice DN may occasionally induce bleeding (see Figure 5(a)), but this does not seem to interfere with the normal regeneration.

One week after the treatment, the regeneration was complete. The synthesis had already finished, and most of the cytoplasm was occupied by contractile apparatus (Figure 5(b)). However, occasional nuclei could be observed centrally (Figure 5(b)). It is also a common finding that some mononuclear inflammatory cells remain when muscle regeneration has ended (Figure 5(b)).

In summary, the repetitive mechanical injury in the muscle fiber performed the classical pattern previously described by the original investigators of the muscular regeneration [7, 8].

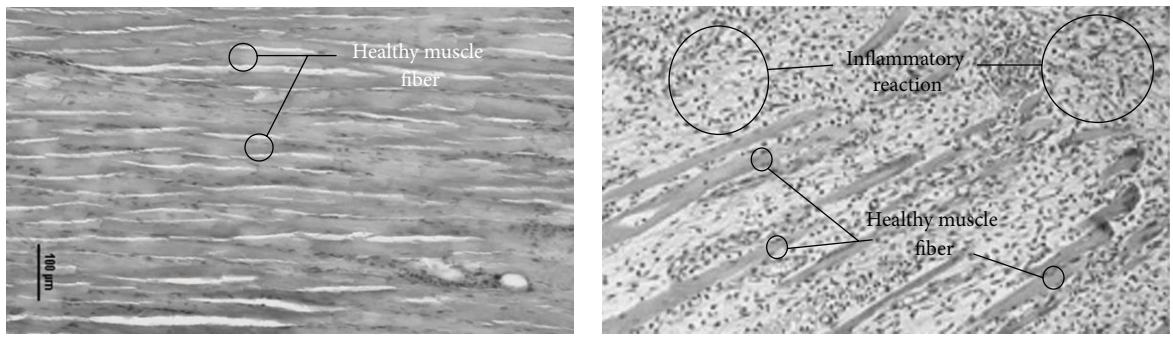
3.2. Nerve Injury. The etiopathogenic explanation of MTrPs involves the neuromuscular synapses [2]. The MTrP is located in the innervation band. Performing DN in skeletal muscles could injure the intramuscular nerves. In our samples, we did not see more than one injury in the same intramuscular nerve branch.

One day after puncture, we observed fragmented axons with the immunohistochemistry stain (Figure 6(a)). The point of injury was higher than the area shown in Figure 6(a). In few hours, the entire region from the point of injury to the synaptic contacts was fragmented.



(a) (b) (c) (d)

Figure 2: DN injury in muscle fibers. (a) DN injury in connective tissue covering the LAL muscle for the first three hours. Sometimes, the extremely superficial punctures affected only the connective tissue. At three hours, we can see an incipient inflammatory reaction. Initial magnification: 200x. (b) DN injury in the LAL muscle during the first three hours. Incipient inflammatory reaction at the edges of the lesion can be seen. Initial magnification: 100x. (c) The inflammatory reaction is already complete after 24 hours. Initial magnification: 100x. (d) The inflammatory reaction coexists with the initial stages of regeneration after three days. The area without cellularity is smaller than that seen in images (b) and (c). Initial magnification: 400x. The four images have been stained with methylene blue.



(a) (b)

Figure 3: Inflammatory reaction. The figure shows healthy muscle fibers (a) and the inflammatory reaction caused by the needle at the third day after treatment (b). Methylene blue stain. Scale bar: 100 μm.

When the fragmentation of axons arrives at the synaptic contact, these synapses will be abandoned. Acetylcholine receptors of the abandoned synapse disperse by the muscle fiber surface. This phenomenon could be observed in our immunohistochemistry images where postsynaptic morphology appeared scattered and unstructured (see Figure 6(b′)). In the third day after puncture, we also found the endplates recently reinnervated by very fine axons covering a spread out postsynaptic component (Figure 6(b), box). During the following days, the receptors would be aggregated below the axon taking the shape of normal adult synapses (see Figure 6(b) circle). At day three after puncture,

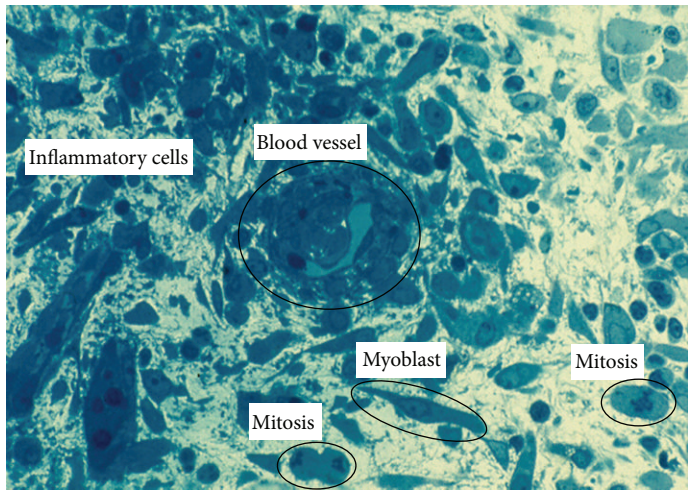
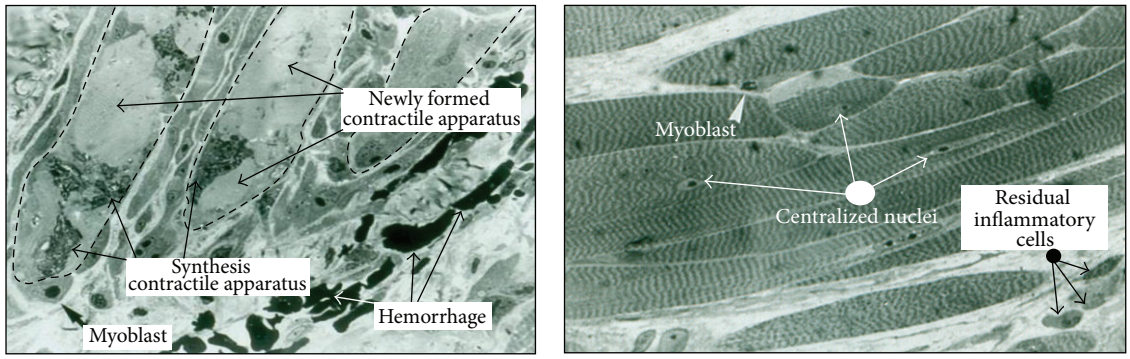


Figure 4: Myoblast proliferation. When the inflammatory cells remove the debris of necrotic muscle fibers, satellite cells are activated and become myoblasts which initiate mitotic proliferation for several hours. Inflammatory reaction, myoblast cells, and mitotic proliferation are coexisting at the same time. Sample was obtained on day three after treatment. Methylene blue stain. Initial magnification: 1000x.



(a) (b)

Figure 5: Muscle regeneration. (a) Myotubes. On the fifth day after puncture, myotubes involved in myofibrillar synthesis can be viewed. Note that there are many areas with newly synthesized contractile apparatus. Some myoblasts have not merged to myotube cells and will become satellite cells in the next days. (b) Young muscular fibers. Seven days after puncture, the DN, signs of degeneration and necrosis are less evident than on day five, and some residual inflammatory cells can be seen. As on the fifth day, some myoblasts attached to the young muscle fibers start regressing to satellite cells. Note that the cytoplasm of the muscle fibers is filled by the contractile apparatus. Some myonuclei definitely remain centralized. Methylene blue stain. Sample included in Spurr. Semithin of 1 μm. Initial magnification: 1000x.

we could see the axonal growth cone as an axonal dilatation beyond its endplate (Figure 6(c)). This growth cone became residual when the postsynaptic component was reinnervated. For several days, we could see receptors scattered in a process of regrouping under fine axons and axonal growth cones. In both cases, these neuromuscular synapses were functional.

Electron microscopy results showed that during the first 24 hours after puncture, myelin disappeared and Schwann cells surrounded axon segments to be digested (see Figure 7(a)). Figure 7(b) shows how Schwann cells occupied the synaptic cleft contributing to the nerve terminal degeneration.

The reinnervation after nerve damage by repetitive mechanical injury was rapid: in three days, neuromuscular synapses were reoccupied.

4. Discussion

In order to analyze the repetitive mechanical injury in the muscle fiber and intramuscular nerve, we analyzed structural changes after 15 repeated punctures (DN) in the LAL muscle. In this section, we compare the DN injury as described by other authors following periods or phases classically described.

4.1. Muscle Damage. Briefly, the usual sequence after muscle injury starts with the inflammatory reaction that removes cellular debris. Then, activated satellite cells, which become myoblasts, initiate a mitotic period. Next, the myoblasts fuse to create myotubes. In the cytoplasm of the myotubes, sarcomeres are synthesized. When the cytoplasm is filled with

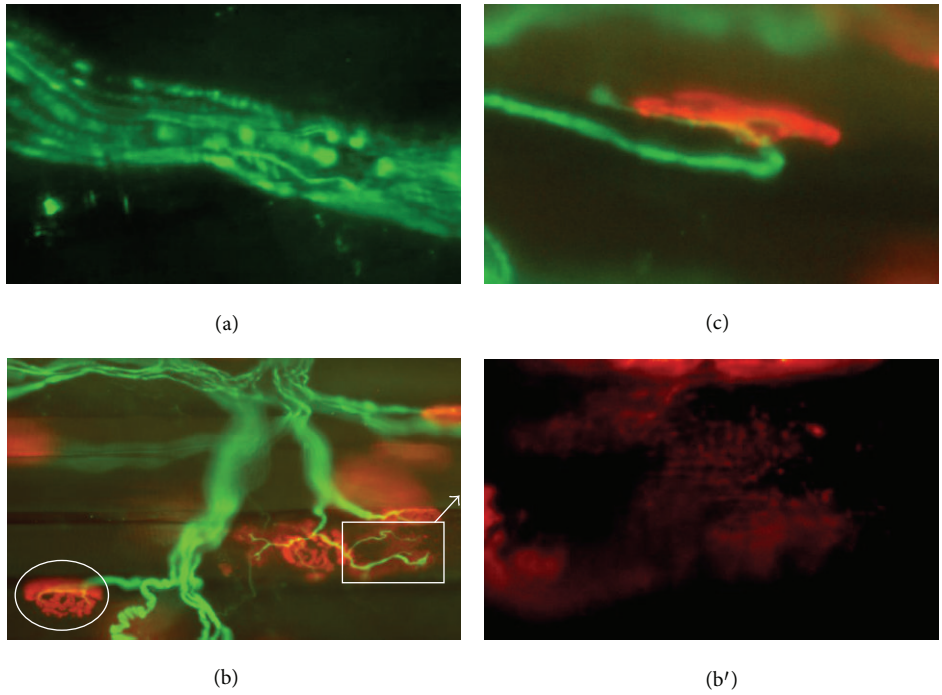


Figure 6: Distal nerve damage by DN. Neurofilament (axon) has been labeled with fluorescein (green) and postsynaptic receptors with α-bungarotoxin rhodaminated (red). (a) Intramuscular nerve shows some axons with fragmented neurofilament. Nerve section due to DN is out of the field, and it cannot be observed in this image. Initial magnification: 600x. (b) The circle shows an example of normal endplate: an axon branched covering postsynaptic component perfectly with compact and defined edges. Inside the box, an example of a recently reinnervated endplate is shown: very thin axon and a dispersed postsynaptic component. Initial magnification: 200x. In (b′), this unstructured component is shown in detail. Initial magnification: 600x. (c) Several days after completion of reinnervation, axonal regrowth can still be seen as in this example: a branch finished in axonal growth cone that runs on the postsynaptic component. Initial magnification: 400x.

sarcomeres, the regeneration is complete [7, 8]. We will follow this sequence to discuss our results.

The type of injury studied in this work (DN action) has not been previously reported. However, our results are similar to those described by other authors with other muscle injuries. In this paper, we compare our results with those analyzing minor injuries. Usually, minor damage to muscle triggers a rapid inflammatory response within the first 24 hours after injury (see Figures 2(b) and 2(c)), for example, physical exercise [21], crush plus heat [22], or chemical injury with bupivacaine ([13]; see also Table 1). However, Allbrook [14] described a mild mechanical injury which did not produce the inflammatory reaction until the fifth day. These authors lightly crushed the muscles with forceps applied for two minutes. We believe that the delay observed in the inflammatory reaction is because this was not a pure mechanical injury and vascular involvement also occurred.

Satellite cells typically reside on the surface of healthy adult muscle fibers. Satellite cells are undifferentiated "sleepers" stem cells waiting for the muscular lesions. When the muscle is attacked, satellite cells become myoblasts [7]. As a result of the inflammatory reaction that follows after minimal lesion, the necrotized part of the sarcoplasm becomes a basal lamina cylinder [23, 24]. The first myoblast within this basal lamina cylinder is described usually about 24 hours after the injury, and then a period of mitoses of these stem satellite cells starts [23, 24]. In this sense, our observations of myoblasts coexisting with the inflammatory reaction are similar to results reported by other authors ([23, 24]; see Figure 4).

Myoblasts from satellite cells initiate a period of mitosis of 9 to 15 hours. The myoblasts resulting from this mitosis period fuse with each other and with the muscle fibers surrounding the area of injury. The resulting structure is a cell called a myotube [7, 8]. In the literature, most studies on muscle injury from exercise show myotubes occurring in a similar period to that obtained in this study (see Figure 5(a)). For example, myotubes can be seen three days after eccentric running exercise in rats [21] or four days after damage induced by lengthening contractions [25].

In the stage of myotubes, actin and myosin are synthesized to create sarcomeres. The synthesis of actin and myosin is called myofibrillogenesis. As described in the literature, the cytoplasm begins to be filled with sarcomeres about four days after exposure to bupivacaine [13] or six days after crush injury [14]. In much more aggressive injuries, such as a complete lesion of the whole muscle, sarcomeres may be observed by day seven [26]. The myofibrillogenesis found in the post-DN treatment is similar in time periods to those obtained with other methods of injury (see Figure 5(a)).

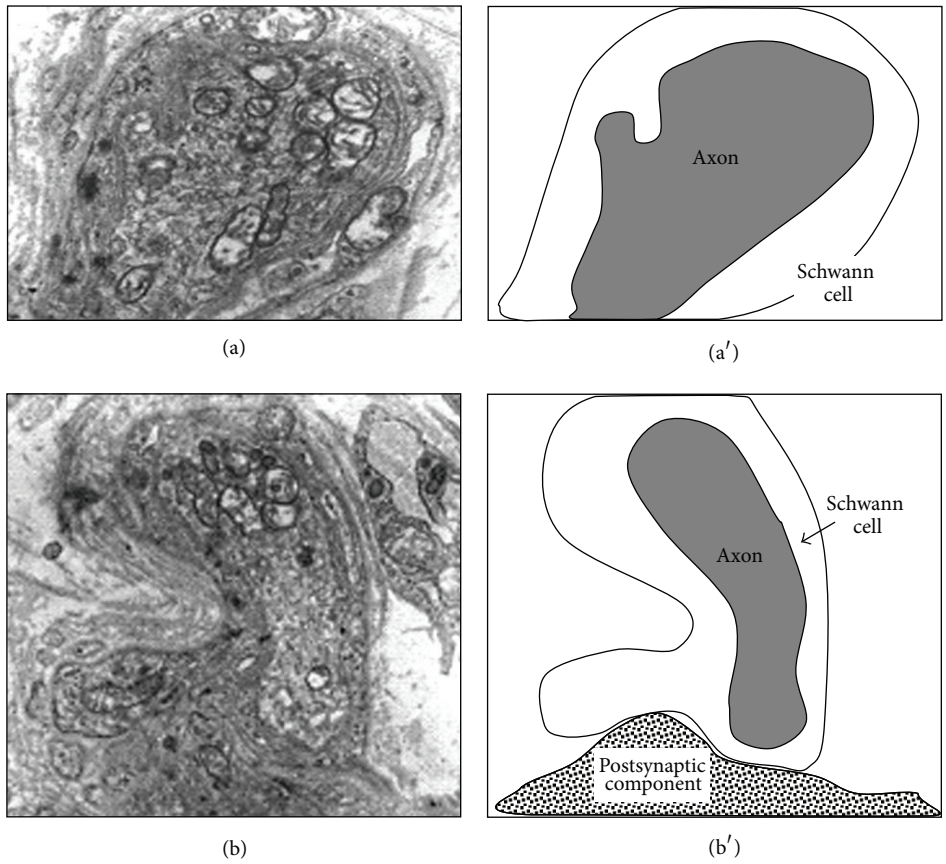


Figure 7: Nerve degeneration and glial participation. Transmission electron microscopy (left) of the first 24 hours after nerve injury accompanied by explanatory diagrams (right). (a) Cross-section of degenerating axon surrounded by a Schwann cell that has lost myelin sheath and is ready for phagocytosis. Initial magnification: 5000x. (b) The terminal Schwann cell completely surrounds the axon terminal and phagocytose. Finally, Schwann cell separates the axon and postsynaptic component. Initial magnification: 5000x.

Some myoblasts (9–12%) remain on the surface of myotubes and involute to satellite cells [7, 8]. This is widely reported in the literature (see Péault et al., 2007 [27] for review), and we can see this at five and seven days after the treatment (Figures 5(a) and 5(b)).

When myofibrillogenesis is almost finished, the morphology of the regenerated area is like the normal muscle fiber: whole cytoplasmic volume occupied by sarcomeres and nuclei extruded to the periphery. However, some centralized nuclei can be observed in the regenerated area. This is a common finding after any muscle injury, also after DN (Figure 5(b)). This myonuclei can remain centralized for several years [28].

After the first few days of intense inflammatory activity, phagocytic cells progressively disappear. However, in the newly regenerated area, some inflammatory cells persist for some time [29]. We can also see some mononuclear inflammatory cells remaining one week after treatment (Figure 5(b)).

Table 1 shows how the type of injury can modify the regeneration steps at different time points. Indeed, each step observed in this work is consistent with the timing previously described by others [13–16].

In summary, the repetitive mechanical injury in the muscle fiber resembles the classical pattern previously described by other investigators in muscular regeneration [7, 8].

4.2. Nerve Injury. As expected, we obtained images of nerve injury with DN. These nerve injuries follow the classic pattern of Wallerian degeneration [10]: initial fragmentation nerve segments, followed by axonal phagocytosis. This phagocytosis at the synaptic level becomes synaptic contact abandoning which produces dispersion of the postsynaptic acetylcholine receptors.

The cascade of events that lead to axonal fragmentation occurs as follows (see Stirling and Stys, 2010 [12], for review): (1) nerve section keeps the distal end without inputs of axoplasmic flow of substances and without axoplasmic transport of organelles; (2) at 24 hours after injury, the distal axonal section already suffers from an energy deprivation; because of a lack of ATP, the ionic pumps (Na^+/K^+, Ca^{2+}) stop working with a net result of an influx of calcium; finally this calcium activates the calpain protease which degrades the axonal neurofilaments [30, 31], and then fragmented axons can be seen. This phenomenon can be observed in Figure 6(a).

Table 1: Some types of muscular injury and degeneration-regeneration times. Some minor muscle injuries were chosen to compare with the DN injury. The degeneration and regeneration periods obtained in this study agree with those previously described for other injury methods. For all items, we considered representative periods of time. For example, for the item "inflammatory reaction," all publications describe when it starts (indicated by the first number) and the day when abundant inflammatory cells are present (indicated by the second number). Ebbeling and Clarkson, 1989 [15]. Chargé and Rudnicki, 2004 [16]. Benoit and Belt, 1970 [13]. Allbrook, 1962 [14].

Muscle/animal	Gracilis/rat	Tibialis anterior and peroneal/mouse and rabbit	Several muscles/human and rodents	Tibialis anterior/rat	LAL/mouse
	[13]	[14]	[15]	[16]	(this study)
Type of lesion	Local exposure to bupivacaine	Crush injury	Exercise	Local exposure to cardiotoxin	Dry needling
Inflammatory reaction	1st day	3rd-4th days	1st-2nd days	6th hour–4th day	1st–3rd days
Satellite cells proliferation	2nd day	4th–6th days	2nd–4th days	2nd–4th days	3rd day
Myotube	3rd day	6th–10th days	3rd-4th days	6th–10th days	5th day
Young muscular fibers	4th day	15th day	6th–30th days	10th day	7th day

Table 2: Minor nerve injuries in the bibliography. We selected studies using nerve injury without separation of the nerve ends, such as crush and neurotoxic. The nerve crush consists of compression with forceps around the nerve for a few seconds. The resultant injury is damaged in all axons without separation of the ends (Lopez-Vales et al., 2008 [19]; Rich and Lichtman, 1989 [17]; Verhaagen et al., 1988 [18]). Similarly, the neurotoxic acrylamide affects all axons without affecting the connective tissue (DeGrandchamp et al., 1990 [20]). Since nerve injury is far from the synaptic contact, some periods are longer than those found in our study. For example, in the report of Lopez-Vales and coworkers [19], the site of sciatic nerve injury was about 45 mm away from the muscle.

Nerve/animal	Nerve of sternomastoid muscle/mice	Nerve of soleus muscle/mice	Sciatic nerve/mice	Sciatic nerve/rat	LAL intramuscular nerve/mice
	[17]	[18]	[19]	[20]	(this study)
Type of lesion	Crush	Crush	Crush	Injection acrylamide	Dry needling
Neurofilament digestion		3th day		4th day	1st day
Phagocytosis of axon	2nd day (area of injury)	6th day (area of injury)	2nd day (area of injury)		2nd day
Reoccupation of postsynaptic component/functional recovery	11th day	8–12 days	21th day	7th day	3th day
Residual growth cones	11th day			7th day	5–7th days

During the first 24 hours after puncture, we can see how Schwann cells surround the axon segments to be digested (see Figure 7(a)). This phenomenon was described previously by Miledi and Slater [32]. During this process, Schwann cells occupy the synaptic cleft contributing to the nerve terminal degeneration as described a long time ago [32, 33] and shown in Figure 7(b). The resulting image of the glial phagocytosis is a synaptic contact abandoned by the axon.

We have obtained an evident dispersion of acetylcholine receptors on the surface of the muscle fibers (see Figure 6(b′)). This phenomenon has already been described by other authors. As described by Thesleff [34], the synaptic component abandoned by degenerated axons cannot maintain aggregation of its postsynaptic receptors. These receptors tend to disperse on the myocyte surface [35, 36]. This situation, called "postdenervation hypersensitivity," consists of an area larger than the synaptic contact and which is sensitive to acetylcholine molecules [34]. However, in our model the reinnervation occurs faster than previously reported (see Table 2).

Finally, the proximal end of the injured axon elongates following the path of the remaining glia to reoccupy its postsynaptic component [37]. The chemical stimulus favors axoplasmic flow and transport, and a distal dilatation that is responsible for axonal growth, called growth cone, appears [38]. When the axons are broken within the muscle by injuries such as exercise, the nerve-muscle contact is quickly reestablished [39]. In the present study, the nerve injury with DN is made within the muscle, and we find the endplates newly reinnervated at the third day after puncture (see Figure 6(b)). Table 2 shows minor nerve injuries in the bibliography. Faster reinnervation is described in this work by DN.

A growth cone beyond its endplate is a common finding after reinnervation and becomes a residual image for several days [17]. We can see this axonal growth cone at day three after puncture (see Figure 6(c)).

Axotomy is a complete nerve section which usually occurs with nerve endings separation (see Bishop, 1982 [11], for review). However, DN induces only a partial lesion of the nerve branch without separation of the ends. The sites of experimental nerve injury are usually extramuscular (see,

e.g., Verhaagen et al., 1988 [18], or Rich and Lichtman, 1989 [17]), which makes both denervation and reinnervation slower than those described in this study. Table 2 compares several results found in the literature with our own results.

The nerve damaged by the repetitive mechanical injury is close to the neuromuscular synapse, and its fast reinnervation follows the classic patterns previously described.

5. Conclusions

These results show for the first time that dry needling produces intramuscular nerve damage. The lesion produced by skeletal muscle dry needling reproduces the same pattern of muscle injury regeneration already described by other authors, showing that repeated muscle punctures do not interfere with the different stages of muscle regeneration and reinnervation.

The aim of our study was to determine the injury caused by DN in muscle and nerve tissues, and consequently we used healthy tissues. Nevertheless, this could be a limitation to our study, since we do not know whether our results could be extrapolated to the pathological tissue of an MTrP. Future research should replicate these experiments either in the existing animal model for trigger spots [40] or in experimentally induced animal trigger spots [41].

Since the real treatment of MTrPs usually involves more than one treatment, future studies should evaluate whether different treatment regimens would also result in regeneration or would give rise to some degree of fibrosis.

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Research Article

Efficacy of Myofascial Trigger Point Dry Needling in the Prevention of Pain after Total Knee Arthroplasty: A Randomized, Double-Blinded, Placebo-Controlled Trial

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The aim of this study was to determine whether the dry needling of myofascial trigger points (MTrPs) is superior to placebo in the prevention of pain after total knee arthroplasty. Forty subjects were randomised to a true dry needling group (T) or to a sham group (S). All were examined for MTrPs by an experienced physical therapist 4–5 hours before surgery. Immediately following anesthesiology and before surgery started, subjects in the T group were dry needled in all previously diagnosed MTrPs, while the S group received no treatment in their MTrPs. Subjects were blinded to group allocation as well as the examiner in presurgical and follow-up examinations performed 1, 3, and 6 months after arthroplasty. Subjects in the T group had less pain after intervention, with statistically significant differences in the variation rate of the visual analogue scale (VAS) measurements 1 month after intervention and in the need for immediate postsurgery analgesics. Differences were not significant at 3- and 6-month follow-up examinations. In conclusion, a single dry needling treatment of MTrP under anaesthesia reduced pain in the first month after knee arthroplasty, when pain was the most severe. Results show a superiority of dry needling versus placebo. An interesting novel placebo methodology for dry needling, with a real blinding procedure, is presented.

1. Introduction

Myofascial pain syndrome (MPS) is a highly prevalent pain condition [1, 2] caused by myofascial trigger points (MTrPs), identifiable as highly localized and hyperirritable spots in palpable taut bands of skeletal muscle fibers [3]. Among many other techniques, dry needling is frequently employed to treat MTrPs [4, 5].

Steinbrocker is usually quoted as the first to describe the effectiveness of punctures without the injection for pain management [6]. Since then, there have been numerous studies showing the effectiveness of dry needling. Some have shown that dry needling is as effective as the injection of various substances for the treatment of MTrPs [7–10].

All available reviews about the effectiveness of dry needling [11–13] reached the conclusion that dry needling appears to be an effective treatment, although studies are needed to elucidate whether its effects are superior to placebo [11, 13]. Due to the invasive nature of dry needling, it is rather difficult to design double-blinded, placebo-controlled studies to analyse its effectiveness [4, 5]. Placebo needles [14, 15] or other sham needling procedures [16] are questioned because they involve some kind of physiological stimulation, which disqualifies them as true placebo interventions [4, 17–19].

In addition, blinding with sham needling is highly dependent on the correct selection of the subjects, whom should be naive to the procedure [15, 16], and on the ability of the clinician performing the procedure [20] giving rise to as much as 20% of subjects unblinded beyond chance.

Some studies claimed to have used a double-blinded, placebo-controlled methodology with placebo needles for the sham needling group, but they elicited local twitch responses in the intervention group without actually assessing the blinding procedure [21]. A local twitch response (LTR) is a brief involuntary contraction of the fibres of the taut band that harbour the MTrP. For a study to be considered double blinded, subjects in all groups of the study must be blinded to group allocation. Since LTRs are unequivocally felt by most patients, it is hard to understand that subjects in the intervention group were really blinded, which adds to the aforementioned blinding limitations of placebo needles.

To avoid these biases, we conducted a randomized, double-blinded, placebo-controlled clinical trial about the effectiveness of MTrPs dry needling in the prevention of myofascial pain after total knee replacement, using a novel blinding methodology.

Total knee arthroplasty has shown to be an effective treatment for knee pain due to knee osteoarthritis, providing patients with improvements in function and in quality of life with low complication rates [22]. It has been reported, however, that in the first month after surgery almost half of the patients have significant pain (>40 in visual analogue scale) [23].

MTrPs are common in lower limb muscles in patients with hip and/or knee osteoarthritis [24], and several papers have emphasized the importance of treating these MTrPs to relieve pain in osteoarthritis of both joints [24–26].

The aim of this study was to find out whether dry needling of MTrPs is superior to placebo in the prevention of pain after total knee arthroplasty, using a novel blinding methodology.

2. Material and Methods

2.1. Research Design. The study was designed as a randomized, double-blinded, placebo-controlled clinical trial. The Ethical and Clinical Research Committee of *Complejo Hospitalario de Toledo* (Spain) approved the study protocol. All subjects were interviewed individually to provide them with details about the nature of the study. All subjects voluntarily signed consent forms prior to entering the study.

2.2. Subjects. Forty subjects were recruited between January 2007 and April 2008. To be included in the study, all subjects had to fulfil these criteria: (1) diagnosis of knee osteoarthritis and scheduled for total knee replacement surgery; (2) presence of active or latent MTrPs in at least one of the muscles included in the examination protocol. Patients were excluded from the study if they (1) suffered from any other condition that could cause myofascial or neuropathic pain in the lower limb, such as lumbar radiculopathy, saphenous nerve entrapment, or meralgia paresthetica; (2) presented any condition usually considered a perpetuating factor of MTrPs, such as fibromyalgia, hypothyroidism, or iron deficiencies [27]. There were no subjects who were excluded based on the study criteria (Figure 1).

2.3. Intervention Description. The study was carried out between January 2007 and October 2008. An experienced and trained physical therapist, blinded to the group allocation, examined the subjects several hours before surgery and at months 1, 3, and 6 after surgery.

Subjects were assigned to a true dry needling group (T) or to a sham dry needling group (S) by using a computerized randomization list (Epidat software program, Xunta de Galicia, Spain).

Immediately after each subject was anesthetized and right before surgery started, a trained and experienced physical therapist applied dry needling to all MTrPs previously identified in the T group, using Hong's fast-in, fast-out technique [3, 28] with 0,30 × 50 mm solid filament needles. The number of insertions of the needle in each MTrP was 20, and the patient position in which every MTrP was needled was the same as the position employed by the blinded examiner for diagnosis (Table 1) and marking of MTrPs. For those MTrPs in the gastrocnemius muscles that were located right behind the knee, dry needling was not applied to avoid injuries in tibial or peroneal nerves. Subjects in the S group did not receive any treatment for their MTrPs. For subjects under spinal anaesthesia in either group (25% in the T group and 35% in the S group), a screen was used in order to prevent the patient from seeing his/her lower limbs. In subjects under spinal anaesthesia in the S group, the physical therapist simulated the application of dry needling without actually applying any treatment. Since subjects could neither see nor feel anything, they were completely blinded to group allocation. Obviously, the physical therapist applying needling was not blinded to group allocation but he did not participate in the data analysis.

2.4. Main Outcomes. The pain visual analogue scale (VAS) [29] was the primary outcome measure. The secondary outcomes measures were the postoperative demand for analgesics, the presence of active or latent MTrPs, the prevalence of MPS, and the Western Ontario and McMaster Universities Osteoarthritis Index questionnaire (WOMAC) [30]. Range of motion (ROM) of the knee and peak isometric strength of knee flexors and extensors was also assessed using a digital inclinometer (12-1507 Baseline, Fabrication Enterprises, Inc., NY, USA) and a digital dynamometer (Microfet 2, Hoggan Health Industries, Salt Lake City, UT, USA) respectively.

During all checkpoints (at months 1, 3, and 6 after surgery), subjects were assessed using all these outcome measures, except for the use of analgesic.

The VAS consisted of a 100 mm line with the endpoints "no pain" and "worst pain imaginable".

Two days after surgery, the use of analgesic medications was recorded for a period of 4 days. Note that during the first two days, all subjects received intravenously applied analgesics consistent with the hospital's standard protocol.

Several hours before surgery, subjects were examined by an experienced physical therapist for the presence of

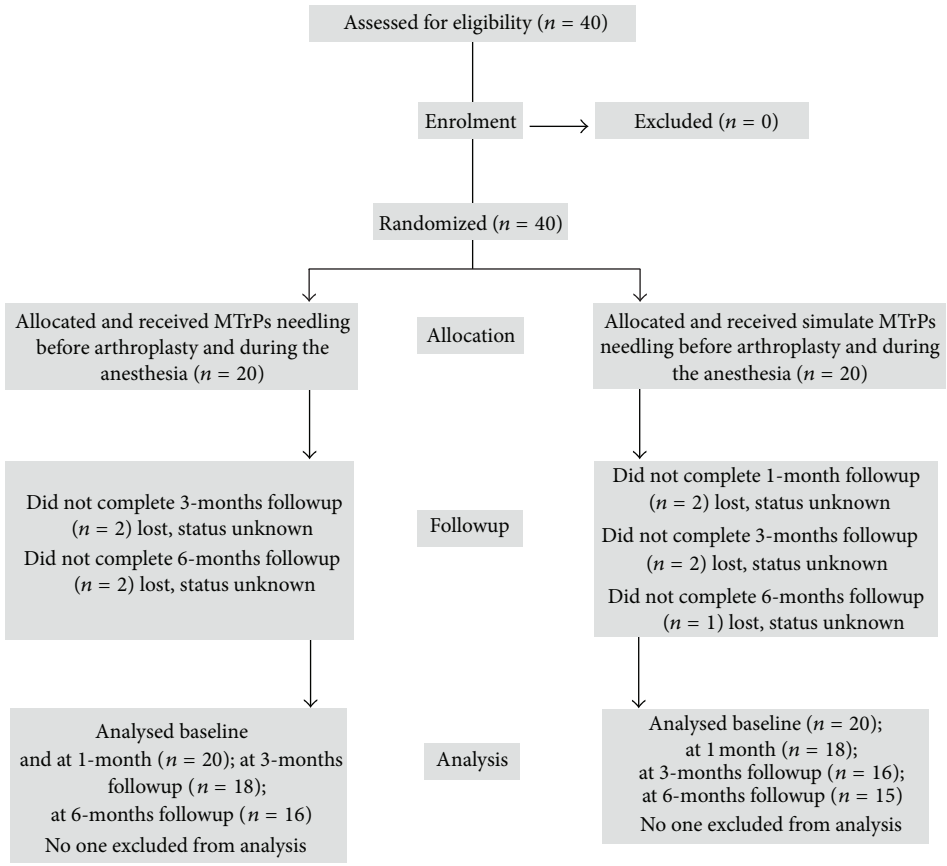

Figure 1: Progress of participants through the study.

Table 1: Examination protocol.

	Tensor fasciae latae	Hip adductors	Hamstrings	Quadriceps	Gastrocnemius	Popliteus
Hip position	Extension Lateral rotation	Flexion Abduction Lateral rotation	Flexion Abduction for medial and adduction for lateral muscles	Flexion	Flexion	Flexion Abduction Lateral rotation
Knee position	Extension	Flexion	Flexion	Flexion	Flexion	Flexion

All muscles were examined with the subject in supine position.

active or latent MTrPs in the muscles of the involved lower extremity using the criteria described by Simons et al. [3]. The tensor fasciae latae, hip adductors, hamstrings, quadriceps, gastrocnemius, and popliteus muscles were examined in each subject as these muscles are frequently involved in myofascial knee pain. The examination of MTrPs followed a strict protocol regarding patient and limb positions (Table 1), the manual examination of each muscle and the marking of the MTrPs with a blue (for latent MTrPs) or red (for active MTrPs) marker. Prior to the start of the study, the researchers agreed upon the MTrPs examination and marking protocols.

In order to establish the prevalence of MPS, patients were considered to suffer from this syndrome if they had at least one active (pain generating) MTrP [3].

The WOMAC is the most widely used instrument to evaluate the symptomatology and function in osteoarthritis of the knee [30]. It contains 24 questions, five about pain (range: from 0 to 20 points), two about stiffness (range: from 0 to 8 points), and 17 about difficulty with physical functions (range: from 0 to 68 points), and can be completed in less than 5 min [31]. An increase in the WOMAC scores (WOMAC pain, WOMAC stiffness, and WOMAC physical function) indicates a degree of deterioration. It has been widely tested in surgical or hospital-based populations and extensively used in clinical trials because of its sensitivity to change and construct validity [31]. The authors of the Spanish version of the WOMAC warn that advanced age of a study population may constitute a possible limitation for its use, which may

be relevant for patients undergoing hip or knee replacement surgery as age does not limit the indication for surgery [30].

2.5. Data Analysis. To assess comparability of the groups at baseline, we used chi-square test (for categorical variables) and Student's t-test (for continuous and ordinal variables). The averages were compared using a Student's t-test. If any of the conditions required for its application was not fulfilled (normality according to the Kolmogorov-Smirnov test and homogeneity of the variances, verified using Levene's test), the Mann-Whitney U test was used. For the proportions we used Pearson's chi-square test to compare treatment groups and the McNemar test to explore change between time points of study. In order to compare variation rate, Student's t-test was used. The Pearson product-moment correlation coefficient was used. To adjust for potential confounding variables, we employed multivariate models (multiple linear regression and multiple logistic regression).

We rejected the one-tailed null hypotheses when the P value was lower than 0.05. The data were analysed using the Statistical Package for the Social Sciences 19.0 (SPSS).

3. Results and Discussion

No complications related to the dry needling intervention were observed in the T group.

3.1. Sample Characteristics. Forty volunteers who were to undergo a total knee replacement procedure participated in the study (29 female and 11 male). The mean (SD) age, height, and weight of the subjects were 72.27 (6.95) years, 1.56 (0.08) m, and 74.75 (10.61) kg, respectively. The rate of women in the whole sample was 70% (55% in the T group and 90% in the S group). The involved knee was the right knee in 60% of subjects (55% in the T group and 65% in the S group). 70% of subjects received general anaesthesia (75% in the T group and 65% in the S group), and in the remaining, 30% spinal anaesthesia was used. The groups were not significantly different ($P \geq 0.05$) in all characteristics (Table 2) except for gender ($P = 0.013$).

3.2. Effect of Dry Needling on VAS Measurements. The initial mean VAS values were higher than the subsequent mean values, which indicates an improvement; this improvement is higher in the T group at the first month, when pain is most severe [23] (see Table 3).

Since the baseline values of the VAS were higher in the T group, we analysed the variation rate (((value at 1 month − baseline value)/baseline value) × 100). The mean value of the variation rate was higher in the T group (−54.50 (56.60) versus −30.47 (63.23) in the S group), and the difference, analysed with Student's t-test, was statistically significant ($P = 0.048$).

A VAS score greater than 40 is considered to represent a significant level of pain [23]. The analysis of this variable (Table 4) showed that before surgery, both groups were similar, although it was slightly higher in the T group. At 1-month follow-up evaluation, the percentage of subjects with a VAS score greater than 40 decreased to 25% from an initial 80% (variation rate = −68.8%). Comparison of baseline values versus 1-month evaluation values of this variable using McNemar test showed that the change was statistically significant in the T group but not in the S group. A comparison of the variation rates of VAS scores greater than 40 between both groups was statistically significant ($P < 0.05$).

Table 2: Preintervention groups characteristics (baseline).

	T group (true dry needling) $n = 20$	S group (sham dry needling) $n = 20$	P value
Age (years)	71.65 (6.06)	72.90 (7.85)	0.570
Body mass index (Kg/m^2)	73.57 (11.53)	75.51 (9.33)	0.580
Days hospitalization	8.11 (1.79)	7.58 (2.04)	0.403
VAS (0–100)	56.75 (22.31)	50.37 (16.76)	0.321
WOMAC pain (0–20)	8.10 (2.45)	7.90 (4.60)	0.837
WOMAC stiffness (0–8)	4.05 (1.61)	3.15 (2.16)	0.805
WOMAC function (0–68)	28.48 (8.54)	27.58 (13.50)	0.149
ROM (°)	89.35 (19.191)	93.20 (20.05)	0.539
Strength FLEX (N)	20.51 (10.16)	22.00 (5.27)	0.565
Strength EXT (N)	24.34 (9.83)	23.42 (7.12)	0.738
MTrPs (number)	12.75 (4.64)	11.75 (3.46)	0.445
MTrPs active (number)	5.15 (4.74)	3.00 (2.83)	0.090

Values are reported as mean (standard deviation). P value obtained using Student's t-test.

Table 3: Initial and subsequent VAS values.

VAS	Baseline	At 1 month	At 3 months	At 6 months
T group				
Mean	56.75	23.80	20.61	23.51
(SD)	(22.31)	(24.86)	(21.49)	(22.50)
n	20	20	18	17
S group				
Mean	50.37	32.30	25.31	20.86
(SD)	(16.76)	(25.72)	(20.03)	(18.58)
n	19	18	16	14
P value	0.320	0.294	0.516	0.725

(SD: standard deviation). P value obtained using Student's t-test.

Table 4: VAS > 40.

Prevalence VAS > 40	Baseline	At 1 month	P value	Variation rate
T group	80.0% $n = 20$	25.0% $n = 20$	0.003	−68.8%
S group	73.7% $n = 19$	47.4% $n = 18$	0.289	−35.7%

Values are percentages. Variation rate = [(percentage at 1 month − percentage at baseline)/percentage at baseline] ∗ 100. P value obtained using the McNemar test.

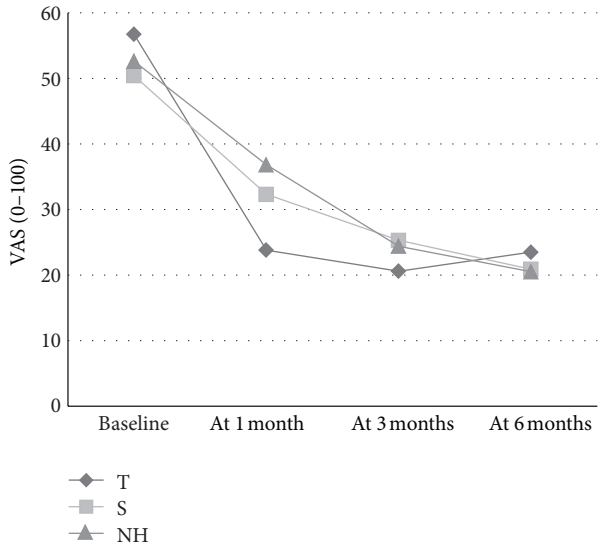

Figure 2: The graph shows average pain scores (VAS) at baseline, and at 1, 3, 6 months in the T group (true dry needling), in the S group (sham dry needling) and in the natural history (NH) [23].

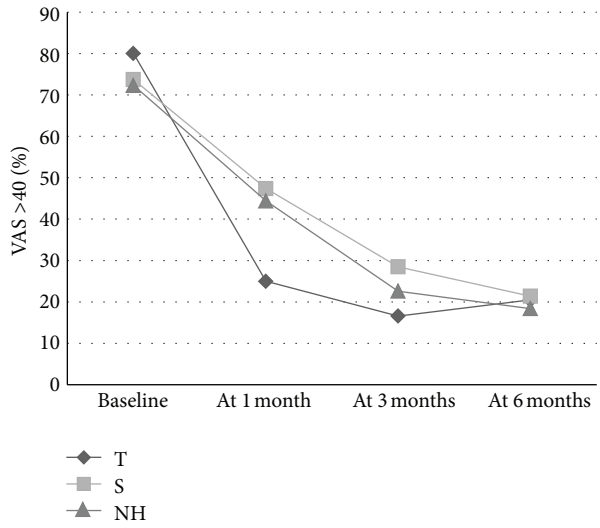

Figure 3: The graph shows percentage of patients with significant pain (VAS > 40) at baseline, and at 1, 3, 6 months in the T group (true dry needling), in the S group (sham dry needling) and in the natural history (NH) [23].

When comparing the outcomes of VAS and VAS > 40 in our study with previously reported results of the natural history of pain after a total knee arthroplasty [23], the results in S group almost completely match those of the results of the natural history (Figures 2 and 3). Figures 2 and 3 also show that subjects in the T group reached the same pain levels in 1-month, as subjects in the S group or subjects with a natural history reached in 6 months.

All subjects had pain before the intervention. In order to find out the percentage of subjects that were pain-free in the different follow-up examinations, variable VAS = 0 was coded and analysed (Table 5). The analysis showed that there was an important difference between both groups at 1-month evaluation, with a significantly higher percentage of pain-free subjects in the T group as compared to the S group.

Table 5: VAS = 0.

Prevalence VAS = 0	Baseline	At 1 month	Variation rate	P value
T group	0.0%	35.0%	−35.0%	0.042
	$n = 20$	$n = 20$		
S group	0.0%	10.5%	−10.5%	
	$n = 19$	$n = 18$		

Values are percentages. P value obtained using Pearson chi-square test. Variation rate was calculated using VAS > 0.

Table 6: Prevalence of myofascial pain syndrome.

	Baseline	At 1 month	At 3 months	At 6 months
T group	80%	50%	50%	59%
S group	70%	59%	53%	64%

Since there were statistically significant differences between groups regarding gender, a multivariate analysis was made (a multiple regression for VAS and a logistic regression for VAS > 40 and VAS = 0) to adjust the effect of the intervention on VAS changes by gender. The inclusion of gender in the analysis did not modify the results in any of the variables. Other variables such as age, BMI, type of anesthesia, and baseline values of WOMAC questionnaire were also included in the multivariate model (not shown here) with no changes observed in significance. Therefore, we did not find any variable that was biasing the results of the analysis.

3.3. Effect of Dry Needling on Analgesics Requirements. The use of analgesic medication was significantly lower in the T group (31.8%) than in the S group (68.2%) using a chi-Square test ($P = 0.01$).

3.4. Correlations between VAS and the Presence of Myofascial Trigger Points. Patients are considered to suffer from MPS if they have at least one active (pain generating) MTrP [3]. In our study, the baseline prevalence of MPS in the whole sample was 75% and decreased much more in the T group (30%) than in the S group (11%), which is nearly a three-fold difference, in the first-month follow-up visit (Table 6). However, despite this difference, the variation rate between baseline and 1-month follow-up visit in both groups was not statistically significant ($P = 0.06$).

MTrPs are persistent sources of peripheral nociceptive inputs, responsible for peripheral [32], and central sensitization [33]. Referred pain from active MTrPs is considered a manifestation of central sensitization [34]. Some studies report a correlation between central sensitization and MTrPs [34, 35] and with knee osteoarthritis [24, 36]. The inactivation of MTrPs and the reduction of referred pain are the results of the desensitizing effects of the treatment. Dry needling causes

Table 7: WOMAC.

	Baseline	At 1 month	At 3 months	At 6 months
WOMAC pain (0–20)				
T	8.10 (2.44)	5.36 (3.85)	4.50 (3.39)	3.24 (3.03)
S	7.90 (3.59)	4.43 (2.99)	3.26 (2.25)	3.13 (2.72)
WOMAC stiffness (0–8)				
T	4.05 (1.61)	2.26 (1.40)	1.94 (1.69)	1.76 (1.52)
S	3.15 (2.16)	2.17 (1.50)	1.87 (1.78)	1.67 (1.59)
WOMAC function (0–68)				
T	28.48 (8.54)	16.94 (10.68)	13.82 (11.48)	9.70 (7.36)
S	27.58 (13.50)	12.92 (8.29)	10.64 (10.42)	10.53 (11.52)

Values are reported as mean (standard deviation). *P* value obtained using Pearson's chi-square test.

Table 8: ROM and strength values at 1-month follow-up examination.

	Group	*n*	Mean	SD	*P* value
ROM	T group	20	74.10	18.80	0.31
	S group	18	77.11	15.31	
Strength FLEX	T group	20	20.49	5.99	0.99
	S group	18	21.25	6.13	
Strength EXT	T group	20	23.01	6.56	0.95
	S group	18	24.11	6.54	

SD: standard deviation. *P* value obtained using Student's *t*-test.

desensitizing effects in patients with MPS [33, 37], which could account for the observed differences between groups, both in the VAS and in the prevalence of MPS.

3.5. Effect of Dry Needling on WOMAC Scores. For all items on the WOMAC, the T group was worse at baseline and throughout all the follow-up checkpoints. Differences between groups were not statistically significant (Table 7). The results of the WOMAC did not correlate with the scores of the VAS, which may be attributed to the difficulty that many subjects experienced with interpreting several test items and completing the WOMAC questionnaires properly. According to Escobar et al., the Spanish version of the WOMAC does have age limitations [30]. They further highlighted that with advanced age, the number of responses to test items and their interpretation may be limited. The mean age of the subjects in the current study was 72.27 (SD = 6.95). In addition, we used the 5-point Likert-type WOMAC questionnaire, instead of the 100 mm visual analog scale format, since, to our knowledge, there was not a validated version of this later format of the WOMAC questionnaire in Spanish. The 100 mm visual analogue scale format has shown a better performance for pain and physical function subscales of the WOMAC questionnaire [38]. These two issues could question the validity of WOMAC results in our sample.

3.6. Effect of Dry Needling on Other Measures. No differences between groups were found regarding results in range of motion or strength in any of the follow-up visits. Table 8 shows these results in the first-month examination. ROM results can be explained by joint limitations due to the arthroplasty and to scar tissue retractions in both capsule and skin. Nevertheless, since MTrPs are considered to limit muscle strength, it could have been expected that the decrease in the number of MTrPs, in the prevalence of MPS, and in pain during the first month would have resulted in an increase in strength that could not be seen in our patients. We only measured the isometric peak value of strength in a single contraction in knee flexion and in knee extension. Further research should employ other outcome measures such as isotonic and endurance measures to evaluate if differences could be detected in this parameter.

3.7. Local Twitch Responses under Anaesthesia. In normal conditions, the rapid needle insertion technique employed in the T group usually elicits brief contractions (LTRs) of the taut band that harbours the MTrP [3]. LTRs are considered to be spinal reflexes [39]. Since our subjects were anesthetized, we did not expect to elicit LTRs during the needling and did not plan any data collection on this issue. Nevertheless, to our surprise, LTRs were elicited in some muscles in most of the subjects in the T group in which spinal anaesthesiology was being used (25% of subjects in the T group) and in one muscle (gastrocnemius) in one of the subjects under general anaesthesia. Unfortunately, we did not collect detailed data about this issue. Although it has been reported that elicitation of these contractions usually correlates with better clinical outcomes of dry needling treatments [7], the type of anesthesia employed in our subjects did not seem to affect the results, probably because of the small number of subjects in which this type of anesthesia was used. Irrespective of its influence in our study, the fact that LTRs could be elicited in patients under anesthesia deserves special attention in future research studies as it could mean that local transmission mechanisms could be more important than usually considered [40].

3.8. Limitations of the Study. The main drawback of this study is the small sample size, which together with the lack of a prior power calculation may have caused type II errors.

The main objective of our study was to compare the effect of MTrP dry needling versus placebo. Nevertheless, our design does not allow differentiating the effect of MTrP

dry needling from the possible neuromodulating effect of the needling itself. Further studies could address this issue using a control group in which needling of the muscle outside the MTrP was applied.

4. Conclusions

A single, brief, and safe dry needling treatment applied under anaesthesia in lower limb MTrPs reduced the pain in the first month after total knee replacement surgery, when pain is highest. Dry needling of MTrPs in the lower limb allowed patients to reach the same degree of pain reduction in 1-month as the subjects with a natural history or placebo intervention achieved in 6-months. It significantly decreased the need for postsurgical analgesia.

This study demonstrates that dry needling is superior to placebo in controlling myofascial pain after a knee arthroplasty. The study introduced a novel placebo methodology for dry needling with a real blinding procedure, which could be utilized in similar studies with different co-morbid conditions, or in studies of myofascial pain concomitant with other surgical conditions of other joints so as to avoid the possible interference of the surgical treatment with the intervention on MTrPs.

Since a single treatment of MTrPs within the context of a knee replacement surgery has proven to be effective in pain reduction after the intervention, it could be conceivable that a more complete treatment program of MTrPs, either before or after the surgery, could be of great help to reduce pain in these patients. Research is needed to test this hypothesis.

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Review Article

Botulinum Toxin for the Treatment of Myofascial Pain Syndromes Involving the Neck and Back: A Review from a Clinical Perspective

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Introduction. Botulinum toxin inhibits acetylcholine (ACh) release and probably blocks some nociceptive neurotransmitters. It has been suggested that the development of myofascial trigger points (MTrP) is related to an excess release of ACh to increase the number of sensitized nociceptors. Although the use of botulinum toxin to treat myofascial pain syndrome (MPS) has been investigated in many clinical trials, the results are contradictory. The objective of this paper is to identify sources of variability that could explain these differences in the results. *Material and Methods*. We performed a content analysis of the clinical trials and systematic reviews of MPS. *Results and Discussion*. Sources of differences in studies were found in the diagnostic and selection criteria, the muscles injected, the injection technique, the number of trigger points injected, the dosage of botulinum toxin used, treatments for control group, outcome measures, and duration of followup. The contradictory results regarding the efficacy of botulinum toxin A in MPS associated with neck and back pain do not allow this treatment to be recommended or rejected. There is evidence that botulinum toxin could be useful in specific myofascial regions such as piriformis syndrome. It could also be useful in patients with refractory MPS that has not responded to other myofascial injection therapies.

1. Introduction

Myofascial pain syndrome (MPS) is defined as a regional pain disorder of muscular origin characterised by the existence of trigger points within muscles. The myofascial trigger point (MTrP) is, in turn, defined as a palpable and hyperirritable nodule located in a taut band of muscle. Stimulation of this point produces two characteristic phenomena: referred pain and sudden contractions of the taut band, called the local twitch response (LTR). Active MTrPs produce pain, and sometimes referred pain, spontaneously. Latent MTrPs produce referred pain as a response to pressure, but not spontaneously.

A current hypothesis is that the disorder underlying MPS is related to inappropriate activity of acetylcholine (ACh) at the neuromuscular junction, which produces a sustained contraction of the sarcomere. The ACh-related effects are relevant to the development of the taut band. This activity leads to an increase in local energy demand or energy crisis [1]. Local muscle pain occurs because of the release of substances from damaged muscle, and from the extracellular fluid around the TrP, such as protons (H+) on acid-sensing ion channels [2], which occurs in ischemia and in exercise [3]. Under these metabolic conditions, sensitising amines that stimulate the nociceptors may be released, giving rise to pain.

There are therefore two phenomena that better define MTrPs: altered ACh activity and nociceptive stimulation [4, 5].

The inappropriate activity at the motor endplate has been studied from an electrophysiological perspective. First, the existence of spontaneous electrical activity (SEA), characterised by continuous low-amplitude action potentials and spikes, was demonstrated in the active MTrP. Excessive ACh activity at the TrP (the muscle endplate) is inferred from the electrophysiologic activity (endplate noise and SEA) [6, 7]. In the other hand, two studies performed on the trapezius muscle identified a significant rise in the concentration of substance P, calcitonin gene-related peptide (CGRP), and other nociceptive neurotransmitters in the biochemical milieu of active MTrP [8, 9].

Another factor that plays a determining role in MPS is the sensitization phenomenon. Persistent peripheral muscle nociceptor activation is converted into a permanent stimulus that facilitates pain neurotransmission. This is due both to a local increase in the number of nociceptors and to the opening of silent multisegment spinal cord circuits [10]. This cytokine activation is critical for central sensitization and glial activation. Glial activation is also important, creating and maintaining enhanced pain states. When glia become activated, pain is amplified [11].

In summary, the disorder underlying MPS is considered to be inappropriate ACh activity at the endplate, producing an energy crisis that favours nociceptive neurotransmitter release. The altered ACh produces active phenomena (taut band), and the nociceptive neurotransmitters initiate the cascade of pain neurotransmission or sensory phenomena: local pain and referred pain.

Botulinum toxin has been used for decades in the treatment of disorders characterised by muscle hyperactivity, such as spasticity or dystonia [12]. Its analgesic potential was observed when, in addition to decreasing muscle hyperactivity, it was found to improve the pain in patients with dystonia [13].

Clostridium botulinum produces seven neurotoxins (designated by the letters A to G). Their best known action is the blockade of exocytosis of the presynaptic vesicles of ACh at the endplate. Two of these neurotoxins, botulinum toxin A (BTA) and botulinum toxin B, are available as biological therapeutic agents and may frequently be used for the treatment of certain conditions involving muscle hyperactivity [14]. BTA is a 150 kilodalton protein formed of a light chain (50 kDa, amino acids 1–448) and a heavy chain (100 kDa, amino acids 449–1280) joined by a disulphide bridge [15].

Botulinum toxin blocks neurotransmission at the neuromuscular junction. Several transport proteins participate in the process by which ACh is released; these proteins aggregate to form the SNARE complex (Soluble NSF (N-Ethylmaleimide-Sensitive Factor) Attachment Protein Receptor [16], responsible for fusion of the vesicles of ACh with the membrane and the subsequent release of the neurotransmitter. The heavy chain of the toxin has a high affinity for the membrane receptors and, once bound, BTA undergoes endocytosis. The light chain is released within the cell, where it acts as a zinc-dependent endoprotease [16–18]. After cleavage of one of the proteins of the SNARE complex by BTA, the complex does not form and ACh is not released.

1.1. Mechanism of Action for Pain Relief. A number of possible mechanisms of action that could explain the antinociceptive effects of BTA have been formulated and investigated [19].

1.1.1. Reduction of MPS-Linked Hyperactivity. In myofascial syndrome it is believed that the excessive ACh production is responsible for the characteristic SEA of MTrPs, detectable on electromyography (EMG). The injection of 10 U of onabotulinumtoxinA (Botox) in the area of the dysfunctional motor endplate was found to reduce SEA in experimental animals [20].

1.1.2. Direct Antinociceptive Effect. It has been shown that BTA directly inhibits the release of pain mediators such as substance P, bradykinin, CGRP, and glutamate [21, 22].

1.1.3. Reduction the Sensitization Phenomenon. Nociceptive sensitization involves an increase in the concentration of substances that facilitate nociceptive neurotransmission, such as substance P, CGRP, and glutamate, both at the peripheral nociceptors and in the posterior horn of the spinal cord. Blockade of the release of these substances peripherally interrupts the first step of sensitization: the accumulation of nociceptive neurotransmitters at the free nerve endings. BTA is therefore considered to be more effective when Sensitization phenomena exist [23, 24] than when they are absent, such as, for example, in acute pain.

As a result, BTA has recognised mechanisms based on experimental studies that would enable it to act on three critical aspects of MPS: excess Ach release, local nociception, and sensitization phenomena. These are the three reasons that have driven research into the analgesic potential of BTA in the myofascial pain syndrome and in other pain syndromes.

1.2. Clinical Experience. The first clinical trial on the treatment of MPS with BTA was published in 1994, and the results were promising [25]. Since that time, almost two decades have passed and many more studies have been published; however, the results have been contradictory, with reports both of nonsuperiority and of superiority of BTA compared with other treatments. A number of systematic reviews have also been published, including meta-analyses, though their conclusions have also been inconsistent.

Given this lack of uniformity or, at least, of similarity between the results and conclusions of those articles, the proposal of the present review is to analyse the publications from a clinical perspective to search for clues that could explain the differences. This is not a systematic review, but rather a critical analysis that aims to examine certain factors that could improve our understanding of the data published to date and of the discrepancies between those data.

The objective of this paper was therefore to conduct a qualitative analysis of the possible sources of variability between the different trials and reviews of the use of BTA for the treatment of myofascial pain syndrome.

2. Material and Methods

Literature searches were performed in the PubMed database using the following key words: "botulinum toxin" "myofascial pain", and "botulinum toxin" "trigger point". The results obtained were filtered to select those clinical trials and systematic reviews that referred to MPS associated with neck or back pain.

The clinical trials were studied from a qualitative point of view, recording specific data on the following aspects: diagnostic criteria, muscles injected, injection procedure, treatment for control group, and outcome measures. All these categories were studied using content analysis to search for possible sources of variability.

The conclusions of the reviews were studied and, after qualitative analysis of each category, a panel of discordant points was drawn up in order to highlight the sources of variability and suggest ways to achieve uniformity.

3. Results and Discussion

Nineteen clinical trials [26–44] and 15 systematic reviews [45–59] satisfied the selection criteria. Tables showing variables studied in every trial has been published previously [48, 50, 51, 58, 59].

Below we describe the possible sources of variability according to the established categories.

3.1. Diagnostic Criteria and Topography of Pain. Given that there is no definitive consensus on the diagnostic criteria of MPS, it is not surprising that studies on the use of BTA for the treatment of MTrPs apply different criteria. There are expert recommendations that propose a series of clinical criteria to make the diagnosis [1, 60]: focal spot muscle tenderness, a taut band running the length of the muscle, pressure-elicited referred pain pattern, pain recognition sign, LTR to stimulation of the muscle by pressure or needling, and other less specific signs, such as regional weakness without atrophy and mild limitation of the range of movement.

Although efforts are being made to establish diagnostic imaging for MPS, particularly with elastography techniques [61], we have still not reached the point at which it is possible to make the diagnosis based on these methods. The combination of signs most widely used in the literature to establish a diagnosis of MPS is the following: tender spot in a taut band, patient pain recognition on tender spot palpation, predicted pain referral on spot palpation, LTR and limited range of movement [62]. Usually, from a treatment point of view, only three criteria are necessary as well as sufficient: taut band, tenderness, and reproduction of pain.

However, the diagnostic criteria used were not detailed in the majority of studies, and it was simply stated that the patients suffered myofascial pain [28, 32, 34, 36]. One study did define two specific criteria to select the MTrPs suitable for injection: the pain recognition sign and pain elimination by compression [37]. Although it is possible to detect percentage improvements in the pain with compression therapy [63], the abolition of pain by compression is not usually considered a diagnostic criterion. Finally, a combination of criteria similar to those previously defined by Simons was detailed in two studies [33, 35].

There was also very marked variability between the trials with regard to the concept of pain topography. It must be realised that although MPS has traditionally been defined as specific to each muscle, it is actually a form of regional or widespread pain [1] and MTrPs can usually be detected in several muscles simultaneously [64]. The majority of studies adopt this approach, selecting patients with headache and neck pain [29, 30], pain in the neck and/or shoulder [34–37], shoulder and arm [33], neck and upper back [32, 44], neck, shoulder, hip or back [28, 36], chronic low back pain [41], or piriformis syndrome [42]. This spectrum of regional pain makes variability unavoidable, both between different studies and within individual studies. One could argue that the trigger point is the same no matter where it occurs and therefore the response to BTA should be the same in any muscle. However, there may be a factor influencing the answer is different depending on the muscles addressed as follows from the fact that some reports for especific muscle syndromes, such as piriformis, are favorable. One factor may be that most studies do not address the entire functional muscle unit involved by trigger points, and therefore, treatment has been incomplete in many studies, affecting the outcome.

An example of how the selection criteria can group together apparently similar but in reality profoundly different samples can be seen if we analyse two of the most detailed studies that have been published to date. In the study by Ferrante et al. there were 142 patients with myofascial pain of the neck or shoulder [37]. The trial by Göbel et al. included 144 patients with myofascial pain of the neck or shoulder [34]. These studies represent the two largest series published in this field. Both used one arm with BTA and another with normal saline. The two series differed in their results and conclusions: the study by Ferrante showed no significant differences between the arm treated with BTA and the one receiving normal saline. The series by Göbel, on the other hand, did detect significant differences in favour of BTA. Up to here the story is perfectly coherent. However, detailed reading of the selection and inclusion criteria of the two studies reveals certain key details. Ferrante applied the following exclusion criteria: (1) a total of more than five active trigger points, (2) more than two trigger points in the trapezius muscle on either side of the body, and (3) more than one trigger point in any other single surface muscle on either side of the body. In contrast, Göbel only included patients if they had at least 10 trigger points. These criteria mean that none of the patients selected by Göbel would have been included in the study by Ferrante as they all had more than 5 MTrPs. Likewise, none of the patients recruited to the study by Ferrante would have been selected by Göbel, as they all had fewer than 10 MTrPs. As a result, two of the largest and most powerful studies published to date were conducted with patients with MPS of such different characteristics that satisfaction of the conditions for recruitment to one trial would mean exclusion from the other.

Another aspect that was not detailed in the studies was whether the syndromes detected in the patients were primary or secondary. Primary MPS is an independent medical entity,

whereas secondary MPS develops in association with other diseases, such as vertebral disc disease, nerve root disease, osteoarthritis, facet joint disease, cervical whiplash or after a muscle lesion [5, 64–66]. These clinical conditions could have affected the final results of the trials; however, they could be helpful to identify subgroups of patients with more or less favourable results.

In summary, the following sources of variability in the diagnosis were detected: lack of uniformity in the criteria used to diagnose MPS, variability in the regional pain topographies included in the studies and in the minimum and maximum numbers of MTrPs in any given patient in order to satisfy the recruitment criteria, and a lack of information about the clinical characteristics of the MPS and possible associated abnormalities.

3.2. Muscles Injected. In view of the diagnostic and topographic variability, we cannot expect greater uniformity in the muscles or muscle groups injected. One aspect that makes it difficult to reproduce certain studies is that the specific muscles injected are not identified in the study reports [30, 31, 34, 37]. Other studies sometimes do not give a complete description; for example, Lew et al. report that the trapezius, levator scapulae, splenius capitis, and other posterior neck muscles were injected [32]. Some studies are more specific, such as the one by Ojala et al., in which it was stated that the injections were made into the trapezius, levator scapulae and infraspinatus [35], and the study by De Venancio et al., in which the masseter, temporalis, occipitalis, and trapezius were injected [29]. Finally some authors state that only one muscle was injected, for example, the infraspinatus [33] or piriformis [39, 42]. Greater detail of the variability may be observed in the case of low back pain; in some studies the lumbar paravertebral muscles were injected [41], specifically the erector spinae [67], whereas other authors recommended the injection of deeper muscles, such as quadratus lumborum, psoas, and piriformis [27, 40, 43].

Such discrepancies in the muscles injected for each pain topography demonstrate either a difference between the different samples or else a difference between authors regarding the muscles considered to be the cause of each patient's pain.

Furthermore, it would probably be difficult to compare the results of studies that injected four different muscles with those that injected only one muscle. The lack of detail about the muscles injected does not help in the interpretation of the data obtained.

There is also the possibility that the treatments could be useful in a specific muscle but not in another. This idea is based on the fact that the studies performed on piriformis syndrome have reported the superiority of BTA while studies performed on another single muscle, infraspinatus [33], have not demonstrated this superiority; this leaves us with a possible source of variability according to the muscle treated.

For physicians familiarised with MPS, the selection of the target muscles for therapy is crucial. Identification of the most important active MTrPs and of other MTrPs in synergic or antagonistic muscles is a determining factor for obtaining satisfactory clinical results [45].

In summary, the marked differences in the selection of the muscle or muscles to be injected constitute another source of variability that could explain the differences in the results between trials.

3.3. Injection Procedure. The myofascial injection procedure is different from any other type of injection, as it requires, insofar as is possible, injection into the nucleus of the trigger point. It means that the needle will be inserted in part of the taut band that is the hardest and most tender, and that gives the most prominent twitch response. A number of techniques have been described to confirm that the injection enters the MTrP: the recommendable clinical procedure requires the LTR to be reproduced on piercing the MTrP. Hong demonstrated that the efficacy of the injection is greater when this response is obtained [68]. The use of a needle connected to an EMG device that enables the SEA to be observed can also be used to confirm that the MTrP has been reached [6]. EMG is seldom done because it is time consuming and costly. Finally, when neither of these methods is available, it is accepted that the needle is close to the MTrP if the corresponding pattern of referred pain is reproduced during the injection.

On this basis, authors have referred to injections "into trigger point" and "nearby trigger point," that is, into the nucleus of the MTrP or close to the MTrP [52]. A third method is used in the muscles in which palpation is less reliable. For example, the psoas is reached using interventional procedures under imaging control, without taking into account where the specific MTrP is located [43].

This is a crucial issue, as the myofascial injection is specific and, as far as possible, must be performed in accordance with the standard procedure described that guarantees closest approximation to the MTrP. However, the majority of studies do not give details of the injection procedure employed and simply state "injection into the MTrP." Some give details of the depth reached with the needle (between 1 and 3 cm) [34]. Others state that the injection was performed using the myofascial technique [29]. Finally, in two studies, it was stated that EMG control was used to locate the MTrP and perform the injection [33, 35]. Some studies have used patterns of fixed points for administration of the toxin, following a grid pattern drawn on the back [44].

Two other very important matters are the *number of trigger points* injected and the *dose of toxin* used. A very wide range of doses and of numbers of injections is reported. With onabotulinumtoxinA, there are studies performed with a single injection [30]. At the other extreme, there are studies with up to eight injections [36]. And in between, we have found studies with four [29–31] or five [37] injections. With abobotulinumtoxinA (Dysport) the number of injections varies between one [28] and 10 [34]. There are also differences in the doses used. With onabotulinumtoxinA, between five and 50 units have been used per injection site. The combination of the dose per injection and the number of points injected give a total dose that varies between 35 U [35] and 250 U [37]. With abobotulinumtoxinA the range was between

25 U [28] and 400 U [34]. The only trial designed to compare different doses of BTA was the one by Ferrante et al., in which onabotulinumtoxinA was used at doses of 10 U, 25 U, and 50 U per MTrP. No dose-dependent effect was observed [37].

There were also differences in the *dilutions* used in the preparation of the medication. OnabotulinumtoxinA is usually used at dilutions of 100 U in 1 to 2 mL, although solution volumes between 0.5 mL [33] and 10 mL [43] have been reported.

The variability in these three aspects—the injection procedure, the number of trigger points injected, and the dose per injection point or total dose—makes it very difficult to interpret the data in a unified manner. Citing once again the two largest trials, there were marked differences between treatments, one with 5 injection sites and a total dose of 250 U of onabotulinumtoxinA [37] and the other with 10 injection sites and a total dose of 400 U of abobotulinumtoxinA [34].

Another procedure-related factor is the *size of the needle* used. Although this might appear less relevant, it has been reported that the results of myofascial injection with local anaesthetic may be better with 21- or 23-gauge (G) needles [69]. Not all authors provide details of the type of needle used, but variability was also observed in those studies in which this parameter was defined, with a range of diameters between 22 G and 27 G [28, 29, 36, 37].

In summary, very significant variations have been detected in the injection procedure. Only a few studies have reported using a standardised procedure to locate the MTrP. The number of MTrPs injected varied considerably, with between 1 and 10 injection sites. There was a sevenfold variation in the total dose of onabotulinumtoxinA between the studies with the lowest and highest total doses, and studies performed with abobotulinumtoxinA presented a 16-fold difference in this parameter. This dose variability makes it very difficult to compare results between trials. There have also been up to 10-fold differences in the dilutions used in the different studies. Finally, the gauge of the needles could also affect results.

3.4. Treatment for Control Group. The control treatment in the majority of studies has been normal saline injection. Almost all authors considered this treatment to be a placebo [34, 37]. However, there is evidence to suggest that the injection of normal saline into MTrPs is not a placebo. Over 50 years ago, Sola et al. published two large series of patients whose pain improved after the injection of normal saline into the MTrPs [70, 71]. Frost et al. performed a study that compared the effect of normal saline and of mepivacaine on MTrPs. He found that patients injected with normal saline improved sometimes even more than those injected with the local anaesthetic [72]. The author concluded that the effect of the needle could probably be sufficient to achieve relief. This effect of saline was confirmed too at the pericranial muscles and tendon insertions for common migraine pain attacks [73].

The effect of dry needling (DN) on inactivation of MPTs is now well known. Many authors have demonstrated the usefulness of DN in MPS [68, 74, 75]. However, few studies have compared DN with BTA. The results suggest that both treatments produce an improvement. In one study there were no significant differences [29], but in another the results of the toxin were superior to those of DN, though similar to the injection of lidocaine [38].

This is an important issue, as the treatments with which BTA has been compared were not placebos but active treatments. Normal saline injection, local anaesthetic injection, and dry needling are all effective procedures, and it must therefore be taken into account that comparative studies using these techniques are trials investigating the superiority of one treatment over another, they are not placebo-controlled trials; this has implications for the determination of study sample size and for the calculation of the expected differences in improvement between the experimental group and the control group.

In addition, certain biases regarding the control treatment must be taken into account. For example, a cost-benefit study that compared the efficacy of BTA versus bupivacaine demonstrated that the two treatments produced similar improvements in the pain but that treatment with the local anaesthetic was much less expensive than BTA [36]. Ignoring the matter of cost, certainly much higher for BTA than for the local anaesthetic, one aspect of patient selection in that study should be noted as it could have favoured the results for the local anaesthetic arm: one of the recruitment criteria was prior successful injection of bupivacaine into the patient's trigger points resulting in more than 50% pain reduction for at least 8 h, but not more than 1 month. As a result, patients had to have responded favourably to one of the future study treatments in order to be included in the study, and this could have favoured that arm.

Other important details that could help to explain the variability in the results of the studies are the concomitant treatments used. For example, in one study, patients in the two treatment arms, BTA and normal saline, also received treatment with amitriptyline, ibuprofen and, when necessary, propoxyphene-acetaminophen. Myofascial release techniques were also applied to all patients for the duration of the study. It is possible that the importance of these associated treatments was not taken sufficiently into account in the evaluation of the improvement achieved in the experimental and control groups [37].

In summary, control treatments considered to be placebos have actually been treatments of known efficacy. In some studies, patients who had previously responded to one of the treatments could have been selected. Finally, some trials have included pharmacological and physical treatments administered concomitantly with the experimental and control treatments and these additional treatments could have masked the improvements observed.

3.5. Outcome Measures. The principal outcome variable in the majority of the studies was the difference between the pain measurements before treatment and during followup. In general, a visual analogue scale (VAS) was used [28, 30, 33, 37], although one study used a four-point pain scale [34]. Also, several standardised methods for measuring quality of life were used, mainly the SF-36 [32, 37, 44].

The majority of the studies reported that BTA was not superior to the treatments with which it was compared [27, 33, 35, 37, 38]. However, there are other high-quality clinical trials in which the opposite result was obtained, and BTA was found to be superior to the control treatment [28, 34, 41, 76]. In fact, in all the studies, all patients injected, whether with BTA or with the control treatment, presented significant improvements in their pain compared to their pretreatment pain levels. However, the pain improvement with BTA was significantly superior to that of the control treatment only in the four clinical trials indicated [28, 34, 41, 76]; in the other studies, BTA was not superior.

In the study by Ferrante et al. [37], it should be noted that although the author did not detect differences in the pain measured using the VAS, there were significant differences in the Role Emotional subscale of the SF-36 and a trend towards improvement in the Vitality and Social Functioning subscales. However, Ferrante considered that this improvement was not evaluable in a context of no improvement in the pain and that it could be explained by a type I error. Notwithstanding, it is interesting to note that other authors have also observed an improvement in the SF-36, in other subscales, specifically in bodily pain and mental health [32], suggesting that the improvement in some quality of life dimensions after treatment with BTA may not necessarily be an error.

Another of the differences detected was in the *duration of follow-up*, which varied between 4 weeks [33] and 6 months [32]. On this matter, it is worth looking at the very detailed and well-conducted clinical trial by Ojala et al. [35]. The outcome measures in that trial were pain measured using a VAS and perceived improvement on a five-point scale. A crossover design was used, in which both groups received both treatments at an interval of four weeks. Thus, the first group received BTA and, four weeks later, normal saline and the second group received normal saline initially followed four weeks later by BTA. The VAS score did not differ between the two groups in either phase of the study. However, the results of the perceived improvement scale at four weeks after the first treatment, before crossover, showed a statistically significant improvement in favour of BTA. This significance disappeared at the end of the second phase, after crossover and reinjection. Data exist that suggest that the effect of BTA persists for 12 weeks. If this is true, the improvement detected after the first treatment period, attributable to BTA, could have persisted during the second 4-week period, after the injection with normal saline, masking the results of the second phase [45].

In summary, there are contradictory results in the different trials in terms of pain improvement, with some trials that do not demonstrate superiority of BTA over alternative treatments and other trials that do confirm the superiority of BTA. Improvements have also been detected in some quality of life measures; these have been considered to be possible errors, but further explanation is required. In addition, there was considerable variation in the times at which the outcomes were measured and this may not have been ideal based on our knowledge of the duration of action of BTA.

The contradictory results in terms of superiority or nonsuperiority of BTA in the different clinical trials are the main source of doubt regarding the true efficacy of BTA in MPS associated with neck and back pain.

4. Systematic Reviews

The use of BT for the treatment of pain of myofascial origin has been analysed in specific systematic reviews and also in joint reviews on the usefulness of BTA in pain [45–59]. As these reviews are based on the clinical trials we have described, they present similarly contradictory results. One of the problems of the reviews could be that the results of studies are considered together regardless of the different approaches and methods used. It has been reported above that these differences are known sources of variability in outcomes and this may be one reason that the reviews provide divergent results and do not provide useful guidance for clinical practice.

The conclusions of the reviewers can be grouped into three types: BTA not recommended, a lack of data to be able to recommend or not recommend the treatment, and recommendation for use in specific conditions.

Some reviews concluded that BTA is not superior to other injection therapies, such as saline or local anaesthetic injection, and that current evidence therefore did not support the use of BTA injection into MTrPs for myofascial pain in general [50, 57] or in cervical [54] or lumbar [55] pain. Those reviewers specifically recommended not using BTA for the treatment of MPS.

Another group of reviewers concluded that the available data were not sufficiently strong either to recommend or to reject the use of botulinum toxin in MPS [51, 59]. In another review, this conclusion was expressed differently, stating that the efficacy remains unproven [56]. Finally, one review maintained both statements in its summary; that is, that there was evidence both for and against its use in myofascial pain syndrome [77]. Recommendations are usually cautious and make reference to suggestions of possible usefulness with some improvement in pain intensity and in the daily duration of pain but with more side effects with botulinum toxin. However these findings provide inconclusive evidence to support the use of botulinumtoxin in the treatment of MPS [46].

Finally, another group of reviewers concluded that botulinum toxin can be useful in MPS in certain clinical conditions.

The first of these involves pain topography. Based on high-quality clinical trials on the treatment of the lumbar pain using the toxin [41], several reviewers recommend the injection of botulinum toxin for the treatment of chronic lumbar pain [47, 56, 57] and piriformis syndrome [48, 56]. In the case of cervical pain, there are also reviews that have concluded that botulinum toxin is probably effective [48].

Another of the clinical situations is the treatment risk of the patient, for example, when the analgesic regimen carries a high potential for adverse effects [49].

One further important aspect is the difference between chronic pain and refractory pain. Refractory pain refers

to pain that does not respond to other treatments. There are clinical trials and reviews that have focused exclusively on refractory pain, that is, on chronic pain that has not responded to other treatments [56, 76].

In summary, the different systematic reviews on the use of botulinum toxin in MPS and in regional axial pain (cervical, lumbar and pelvic) associated with this diagnosis, vary from no recommendation for use, through the absence of a recommendation in favour or against, or finally, to use only in specific conditions: pain refractory to treatment, and pain at specific sites (cervical, lumbar, and pelvic).

5. Conclusions

The use of botulinum toxin in MPS has a pharmacological and pathophysiological basis. In MTrPs there is excessive Ach release and an increase in the concentration of nociceptive neurotransmitters in the biochemical milieu of the MTrPs. BTA appears to be effective on both targets, reducing ACh release and blocking nociceptive neurotransmission.

This rational basis has been the justification for a number of clinical trials, but there are marked discrepancies between the results of those trials. Looking at the most important ones, some do not demonstrate the superiority of BTA over other treatments [27, 33, 35, 37, 38] whereas others did find differences in favour of BTA [28, 34, 41, 76].

In this paper, content analysis has been used to scrutinise the trials from a clinical perspective in order to identify sources of variability that could explain the differences in the results. The most significant findings were the following.

(i) Diagnostic selection and criteria: the trials have used different diagnostic criteria for MPS. There is insufficient standardisation of the different topographies of pain, with studies that have focused on a single area of the vertebral column and others that include several areas. In addition, there are very relevant discrepancies in the number of MTrPs treated and a lack of information on clinical characteristics, such as the type of myofascial pain and its associated abnormalities. The selection criteria for some studies would have led to the exclusion of their patients from other studies [34, 37].

(ii) Muscles injected: in general, the different studies do not coincide in the target muscles. Even in patients with the same pain topography, different muscles were injected. And in some studies, the muscles treated were not even mentioned.

(iii) Injection procedure, number of trigger points injected, and dose used: in many studies, it was not stated whether a myofascial type injection procedure was used, with robust criteria for injection into or nearby the MTrP. The number of trigger points treated showed little uniformity, as between 1 and 10 were injected, depending on the study. The doses used varied by up to 16-fold between the trials with the highest and lowest total doses. There was also variability in other factors, such as the dilution and the type of needle used.

(iv) Control group treatments: the groups treated with placebo received treatments of known efficacy, such as normal saline, local anaesthetics, or dry needling. The investigations were therefore comparative studies between two treatments rather than an experimental group versus placebo.

(v) Outcome measures: the results of the trials are contradictory. In some, superiority of BTA over other treatments was not observed whereas others reported the superiority of BTA. Improvements were also detected in some quality of life measurements, and these require further explanation. Finally, the length of followup was often suboptimal if the duration of the effect of botulinum toxin is taken into account.

These marked differences have led reviewers to reach contradictory conclusions: BTA not recommended, neither recommended nor rejected or, finally, recommended for use in specific conditions of refractory pain or for pain with a specific topographic diagnosis.

5.1. Recommendations: to Inject or Not to Inject. The contradictory results in terms of superiority or nonsuperiority of BTA in the different clinical trials are the main source of doubt about the true efficacy of BTA in myofascial pain syndrome associated with neck and back pain.

In reality, no study has demonstrated that BTA does not improve a patient's pain. In all of them, the pre- and post-treatment outcome measures showed significant improvements. What has not been possible to demonstrate in some studies is the superiority (or inferiority) of BTA versus other treatments.

To resolve these issues, further studies must be performed that take into account these and other sources of variability described in the literature [45, 46]. The studies must apply strict criteria for the diagnosis of MPS and must evaluate the basic clinical parameters of the MTrPs. Strategies for a uniform injection technique (fixed sites) or techniques based on the patient's symptoms (follow the pain) could be established in order to identify the best approach for research. The injection procedure should be strictly myofascial and should include the use of systems available to confirm that the injection has been made into, or at least nearby, the MTrP (stimulation of LTR, SEA detection on EMG or the induction of referred pain in active points). When calculating the sample size, it must be taken into account that control treatments with local anaesthetic or normal saline are not placebos, or else a true placebo must be designed for the trials. The duration of followup for the outcome must be optimised and should probably continue for between 3 and 6 months.

In addition, in the light of all these findings, it must be concluded that there are insufficient data either to recommend or reject treatment with BTA in MPS. Many reviews close with this statement after an extensive analysis and the use of complex statistical methods, and physicians who study those reviews may therefore be left with an uncomfortable feeling that their reading has not helped to resolve the complex task of clinical decision taking.

Although this is a particularly controversial subject, some additional arguments may perhaps be given. At the present time, the treatment of MPS with BTA is an off-label indication. Some trials conclude that BTA is neither superior nor inferior to other treatments injected into the MTrPs, whereas other trials show that BTA is superior to other injection treatments. There is evidence that BTA could be useful in at least some subgroups of patients in which the most relevant characteristic is therapeutic refractoriness [56]. Some specific myofascial topographies, such as piriformis syndrome, may show a more favourable response [39]. Following this line of discussion, and complying with local regulatory procedures for off-label use, it may not be unjustified to offer this treatment to patients with refractory MPS that has not responded to other forms of injection therapy. If it is decided to use this approach, all these details must be explained to the patient by means of an informed consent. Under these conditions, the feeling of some physicians is that treatment with BTA may be helpful to the group of patients that does not respond to other myofascial treatments.

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Review Article

Probable Mechanisms of Needling Therapies for Myofascial Pain Control

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Myofascial pain syndrome (MPS) has been defined as a regional pain syndrome characterized by muscle pain caused by myofascial trigger points (MTrPs) clinically. MTrP is defined as the hyperirritable spot in a palpable taut band of skeletal muscle fibers. Appropriate treatment to MTrPs can effectively relieve the clinical pain of MPS. Needling therapies, such as MTrP injection, dry needling, or acupuncture (AcP) can effectively eliminate pain immediately. AcP is probably the first reported technique in treating MPS patients with dry needling based on the Traditional Chinese Medicine (TCM) theory. The possible mechanism of AcP analgesia were studied and published in recent decades. The analgesic effect of AcP is hypothesized to be related to immune, hormonal, and nervous systems. Compared to slow-acting hormonal system, nervous system acts in a faster manner. Given these complexities, AcP analgesia cannot be explained by any single mechanism. There are several principles for selection of acupoints based on the TCM principles: "Ah-Shi" point, proximal or remote acupoints on the meridian, and extra-meridian acupoints. Correlations between acupoints and MTrPs are discussed. Some clinical and animal studies of remote AcP for MTrPs and the possible mechanisms of remote effectiveness are reviewed and discussed.

1. Introduction

1.1. Myofascial Pain Syndrome (MPS). Myofascial pain syndrome (MPS) has been defined as a regional pain syndrome characterized by muscle pain caused by myofascial trigger points (MTrPs) [1]. Clinically, MPS includes any pain phenomenon due to activation of latent MTrPs as a consequence of a certain pathological conditions including chronic repetitive minor muscle strain, poor posture, systemic diseases, or neuromusculoskeletal lesions (such as sprain, strain, bursitis, enthesopathy, arthritis, and vertebra disc lesion) [2–4].

1.2. Myofascial Trigger Point (MTrP). MTP is defined by Travell and Simons [1, 5] as the most tender (hyperirritable) spot in a palpable taut band of skeletal muscle fibers. Pressure stimulation of a typical MTrP can elicit pain, referred pain, and local twitch response (LTR) (brisk contraction of muscle fibers in its taut band). The pain elicited by compression of this spot is familiar to the patient as the usual pain complaint (pain recognition) [5]. It has been suggested that "spot tenderness", "taut band", and "pain recognition" are the three important criteria for the diagnosis of MTrP, and "referred pain" and "local twitch responses" can be "confirmatory signs" for MTrP diagnosis [6].

A myofascial pain patient may have both latent and active MTrPs. Latent MTrPs can be identified in most normal adult skeletal muscles and they are tender, but not painful spontaneously [1]. Active MTrPs are painful spontaneously or in response to movement of the involved muscle. In clinical observation, if a latent MTrP is not appropriately treated or the associated underlying pathological lesion is not eliminated, it can be activated to become an active MTrP, or the pain region may expand to other regions and develop other active MTrPs [4, 5]. The original MTrP is called primary MTrP or key MTrP, and the later developed MTrPs are secondary MTrPs or satellite MTrPs [5]. Inactivation of

a key MTrP can subsequently eliminate the satellite MTrPs [5, 7]. It has been hypothesized that there are multiple MTrP loci in an MTrP region [3, 7]. An MTrP locus contains a sensory component (sensitive locus or LTR locus) and a motor component (active locus or spontaneous electrical activity locus).

1.3. Treatment of Myofascial Trigger Point. Appropriate treatment to MTrPs can effectively relieve the clinical pain of MPS. The most important strategy in MPS therapy is treating the underlying etiological lesion that causes the activation of MTrPs [2, 3, 5–8]. If the underlying pathology is not appropriately and completely treated, the MTrP can only be inactivated temporarily and never completely. Conservative treatment, such as appropriate systemic nonsteroidal anti-inflammatory drug (NSAID) or local NSAID gel or patch, thermotherapy, manual therapy, and other physical modalities, should be performed prior to more aggressive therapy, such as local steroid injection, spinal facet joint injection, MTrP injection, dry needling, or acupuncture (AcP), especially for acute lesions or mild lesions [2, 3, 5, 8–10]. It is important to eliminate any perpetuating factors causing persistent existence or recurrence of active MTrPs, and to provide adequate education and home programs to patients to avoid recurrent or chronic pain [5].

2. Hypothetical Pathophysiological Mechanism of the Myofascail Pain Syndrome

2.1. Etiology of Myofascial Trigger Point. There is general agreement that acute muscle overload can activate MTrPs. MTrPs due to muscle overactivity can be easily inactivated after avoidance of overuse or inappropriate use. If an acute lesion is not well controlled (usually due to repeated injury, a severe tissue damage, or inadequate treatment), it can become a chronic lesion with progressive scar tissue formation. This scar tissue may be the major cause of degenerative lesions, which could be a source of MTrP activation in later life [11, 12].

Most adults have latent MTrPs in most skeletal muscles that can become active in response to any related lesion in another site. A recent study found that every adult had a hyperirritable spot in the brachioradialis muscle, which could be a latent MTrP, or in the vicinity of the latent MTrP, but no latent MTrPs in children under the age of 1 year [13]. It appears that MTrP circuits in the spinal cord develop in later life when the child is growing up. In a later study, Han and her colleagues [14] found that a child had increased sensitivity at the tendon attachment site and the muscle belly after age of 4 years. They concluded that a child might develop an attachment trigger point and a latent MTrP at the brachioradialis muscle after the aged 4 years. Degeneration may develop at middle age or even younger if previous injury was severe or not treated appropriately. A degenerative tissue is vulnerable to reinjury, especially in the elderly or in a weaker tissue. Therefore, appropriate treatment of an injured soft tissue lesion may be important in avoiding chronic myofascial pain.

2.2. Integrated Hypothesis of MTrP. Integrated hypothesis of MTrP, postulated by Simons and Travell [15], have three essential features (excessive acetylcholine release, sarcomere shortening, and release of sensitizing substances) [16]. An increased acetylcholine release in the neuromuscular junction (motor endplate) can cause an increase of the muscle fiber tension (taut band) that containing an MTrP, and subsequently can cause "energy crisis" with increased metabolism and local ischemia and hypoxia which can induce secretion of sensitizing substances to cause pain. The sensitizing substances can further cause abnormal acetylcholine release so that a vicious cycle is completed [16]. It has been suggested that the MTrPs appear to be located in the endplate zone of the affected muscle fibres, where there was increased spontaneous electrical activity and signs of peripheral sensitization of sensory nerves, as well as the appearance of contractures. Excess microendplate potentials result in a sustained alteration of the membrane potential of the muscle fibres around the endplate, and this may result in dysfunction of endplate, and Ca leak from ryanodine channels in the sarcoplasmic reticulum. This would be consistent with sarcomere shortening in a region close to the endplate [15–17].

Irritation or sensitization of nociceptors can cause spontaneous pain. Central sensitization may be the main cause of MTrP activation related to a remote lesion and may also cause spontaneous pain without stimulation to the nociceptors. Nociceptors in an MTrP region connect to a group of dorsal horn cells (sensory neurons) in the spinal cord. These "MTrP related sensory neurons" are responsible for central sensitization and for transmission of pain information to the brain. The neural network with connections among these "MTrP related sensory neurons" is defined as an "MTrP circuit" [2, 8]. An MTrP circuit corresponding for a certain MTrP can also send nerve branches to connect with the other MTrP circuit corresponding to other MTrPs. A latent MTrP may become active if stimuli from peripheral sites are strong enough to trigger the MTrP circuit of this latent MTrP. Most adults have latent MTrPs in most skeletal muscles that may become active in response to any related lesion in another site. The "MTrP Circuit" for an MTrP may be responsible for all MTrP phenomena including pain, referred pain, local twitch response, motor dysfunction, and autonomic phenomena via the spinal cord reflex [4, 18].

3. Needling Therapy for Myofascial Pain Syndrome

3.1. Definition of Needling Therapy. Needling therapy means any treatment with needles. "Dry needling" is defined as the penetration of a needle through the skin without introduction of any drug, and "injection" is the procedure of needling therapy with introduction of drugs via an "injection needle" (containing a central hollow). Using a solid needle without central hollow or an injection needle with a central hollow can perform "Dry needling". Kalichman and Vulfsons [19] suggested that dry needling is a cheap, easy to learn with appropriate training, caring lower risk, and minimally invasive treatment modality.

3.2. Injection for Myofascial Pain. The traditional MTrP injection technique (multiple needle insertions) is originally described by Travell and Bobb [20]. The needle is moved in-and-out into different directions to encounter the sensitive loci in an MTrP region. In this way, MTrP pain can usually be eliminated nearly completely immediately after most of those multiple sensitive loci have been injected with a drop of local anesthetic agent on each site. Hong [21] has modified this technique to a fast-movement procedure in order to avoid tissue damage from side movement of needle or the grabbing of needle by an elicited LTR. Later, this new technique has been recommended by Simons et al. [5] and have been widely use for trigger point injection or needling.

3.3. Other Types of Needling Therapies for Myofascial Pain. Fischer [22] suggested infiltrating with local anesthetic into the whole taut band including the myotendonal junction during MTrP injection, and performing "Preinjection blocks" to reduce the pain of needle penetration. Gunn used an AcP needle [23], and Chu [24] used an EMG needle, to perform dry needling to avoid the tissue damage by the sharp edge of the injecting needle. Furthermore, Chu et al. [25, 26] added electrical stimulation during treatment ("electrical twitch-obtaining intramuscular stimulation" or "ETOIMS") in this technique, which is actually similar to electrical AcP. The technique of superficial dry needling (inserting the needle into the subcutaneous, but not the muscle tissues) has been demonstrated to be effective for treating myofascial pain [27–29]. Several authors have demonstrated the therapeutic effectiveness of pain control by MTrP injection with botulinum toxin A [30–32]. But the latest Cochrane review [33] suggested that there is inconclusive evidence to support the use of botulinum toxin in the treatment of myofascial pain syndrome.

3.4. Modified Acupuncture Therapy. Recently, Chou et al. [34] have developed a new technique of AcP therapy, which is similar to MTrP dry needling by insertion of the AcP needle into multiple sites of the MTrP region with a fast insertion speed (high pressure) to elicit LTRs. Simultaneous rotation of the needle (fast screwed-in and screwed-out technique) is also performed to facilitate the needle movement and to avoid bending of the small-sized AcP needle. In a related recent study on its therapeutic effectiveness, it was found that the irritability (measured as subjective pain intensity, pain threshold, and amplitude change of EPN) of the MTrP in the upper trapezius muscle could be suppressed after needling remote AcP points [35].

4. Probable Mechanism for Acupuncture in Pain Control

4.1. Chinese Traditional Acupuncture. Chinese traditional acupuncture is probably the first reported technique in treating patients with dry needling based on the Traditional Chinese Medicine (TCM) theory and has been commonly accepted for pain alleviation (analgesia) since 2500 years ago. TCM is a complex theory. In TCM concepts, the entire human body is composed of sophisticated interconnected inner systems, which there is an "energy (Qi)" that flows through "meridian (or channels)" in each organ [36, 37]. When the flow of Qi is blocked, pain and disease occur. By inserting and appropriate manipulating a needle into some points, the channel could be unblocked, thereby reestablishing the free and normal flow of Qi and relieving the pain. Most acupoints are located along one of these channels (some are exceptional). Diseases are caused by an imbalance or disturbance of Qi. Needling at the acupoints can harmonize Qi and treat diseases. These systems should be kept in balance to maintain a good health [36, 37]. These hypotheses, however, have not yet been validated by modern science and technology.

4.2. Acupuncture Analgesia. AcP has been widely used for treating patients with acute or chronic pain. Many comprehensive review articles on AcP analgesia have been published in recent years [38–41]. The mechanism of AcP analgesia has been widely explored since the 1970s, but still has not been adequately clarified. Many efforts have been made to clarify the mechanism of AcP analgesia, but no satisfactory consensus has been reached to date.

4.3. Endogenous Opiates (Morphine-Like Substrate) Theories. One Study for time-dependent analgesic effect in healthy humans was performed in the 1970s [42]. It showed that manual AcP at one hand acupoint induced a gradual increase in skin pain threshold and faded after removal of the needle. The effect was totally abolished after the infiltration of the local anesthetic procaine deep into the acupoint at the muscle and tendon layer, but not subcutaneously. The most well-known mechanism of AcP analgesia is the endogenous opiates (morphine-like substrate). Pomeranz and his colleagues [43, 44] have suggested that electroacupuncture (EAcP) induces endogenous opiates release from the pituitary gland into plasma and cause analgesia in the central nerve system. The followed researches disclosed that different kinds of endogenous opiates, such as β-endorphin [45, 46], enkephalin [46, 47], endomorphin [48], and dynorphin [49] also play very important roles for AcP analgesia. Cheng and Pomeranz [50] first described the possibility of different analgesic mechanism for different frequencies of EAcP. Later in Han JS's research group, they found that different types of opioid receptors mediated analgesia induced by EAcP of different frequencies [51]. More recently researchers claimed that the frequency is not the only determinate factor for analgesic effect. Lin et al. [52] found that intermittent-alternating mode of administering EAcP stimulation is a valid way to prevent tolerance. Lao and his colleague [53] systematically evaluated the antihyperalgesia of EAcP stimulation parameters (frequency, intensity, treatment duration, and pulse width) and suggested that the EAcP antihyperalgesia is parameter-dependent and point-specific.

4.4. Serotoninergic Descending Pain Inhibitory Pathway Theories. In addition to the opioids, serotonin (5-HT, 5-hydroxytryptamine) had been speculated to be an analgesic

transmitter in Cheng and Pomeranz's [50] early study and thought to play an important role in AcP analgesia. Tsai and his colleagues [54] conducted a rat study to find the possible mechanism of EAcP in reference to the effects of neuropeptides on serotonergic neurons and suggested that the influence of EAcP on 5-HT release may be due to activation of enkephalin-interneurons, which presynaptically inhibit the primary sensory neurons in the spinal cord. To elucidate which serotonin receptor subtypes involved in modulation of EAcP, Takagi and Yonehara [55] examined the inhibition effects of EAcP after different serotonin antagonists intravenous injected into rabbits and found that the 5-HT_{2A} receptor may be involved in modification of the transmission of the pain sensation through activation of excitatory pathways, and 5-HT_{1A} receptor activation may suppressively act on EAcP-induced analgesia. In a later study of Chang et al. [56], they found that the EAcP analgesia effect is blocked by 5-HT_{1A} and 5-HT_3 antagonists at both low and high frequencies and enhanced by 5-HT_2 antagonists at high frequency (100 Hz). Furthermore, serotoninergic descending pain inhibitory pathway theories have been also developed. There are many serotonin-releasing nuclei in the central nervous system. Raphe-spinal neurons were identified in the nucleus raphe magnus (NRM), which is one of serotoninergic neurons in the lower brainstem and the axons of them terminate at the level of spinal cord. Liu and his colleagues [57] found EAcP could activate these serotoninergic raphe-spinal neurons in the NRM, a supraspinal area mediating a negative feedback circuit of pain modulation, thus inducing analgesia via descending inhibition. It is also an excitatory receptor in the cortex and the hippocampus. Higher frequency EAcP might decrease the serotonin concentration within the cortex, acting as a sedative, then elicit analgesic effect via both the descending pain inhibitory pathway and the cortex [38].

4.5. Anti-Inflammatory Mechanism. In the 1990s, researchers conducted studies using inflammatory animal models [58, 59] and found AcP analgesia may be related to anti-inflammatory mechanism. More peptides (substance P, somatostatin and calcitonin gene-related peptide), which related to pain transmission, can be expressed after neurons have been injured [60]. With persistent inflammation, it can induce the hyperalgesia status (hyperexcitable to pain), then decrease pain threshold. If the peripheral tissues have been inflamed, some immune cells can excrete endogenous opiates that can bind with opioid receptors on peripheral afferent nerves [61], and then can inhibit the transmission of noxious signal from the peripheral nerve system to the central nerve system. In Sekido's study [58], they have suggested that peripheral opioid receptors are involved in EAcP analgesia during inflammatory conditions via local blockade instead of systemic blockade of opioid receptors. EAcP produces antinociception via release of endogenous opioid peptides, and then reducing the sign of hyperalgesia associated with inflammation [59].

4.6. Cholinergic Anti-Inflammatory Pathway. To date, there was debate about whether endogenous opiates act as neurotransmitters or hormones. Lin and Chen [38] have declaimed a "neuroimmune link", which can answer for this argument well. Within central nerve system, endorphins are neurotransmitters, and within peripheral tissue, they are hormones. Inflammation is a local, protective response to microbial invasion or injury. The body's first defense against invading pathogens or tissue injury is the innate immune system. Tracey [62, 63] has reported that the cholinergic anti-inflammatory pathway is a neural mechanism that suppresses the innate inflammatory response. The nervous system reflexively regulates the inflammatory response and modulates immune responses in real time. This is the first time to postulate that the relationship between AcP and the anti-inflammatory reflex is mediated through the autonomic nerve system [62] and offer a unique opportunity to explore previously unrecognized techniques to treat disease and enable consideration of the neurological basis of complementary and alternative medical therapies, such as meditation and AcP [63].

4.7. Summary. According to these above researchers, Lin and Chen [38] have suggested that the analgesic effect of AcP is hypothesized to be related to immune, hormonal, and nervous systems. Compared to slow-acting hormonal system, nervous system acts in a faster manner. Given these complexities, AcP analgesia cannot be explained by only one single mechanism.

5. Needling (Including Acupuncture) for Pain from MTrPs—Clinical Trials and Basic Research

5.1. Clinical Trials of Dry Needling for MTrPs. Although the analgesic mechanism of dry needling (including AcP) effect is still not well known, the practice of inserting needles into soft tissue tender points to alleviate pain is well accepted. The clinicians commonly adopting the orthodox of injection, dry needling, or the traditional AcP. In one of the early studies investigating dry needling for trigger point, Lewit [64] conducted a study investigating short- and long-term effects of dry needling in the treatment of chronic myofascial pain. Effectiveness for alleviating chronic myofascial pain was noted, and the immediate analgesia produced by needling the pain spot has been called the "needle effect". It is still unclear if the MTrP injection can also provide significant needle effect. Many authorities strongly believe this possibility [7, 65, 66].

Cummings and White [67] conducted a systematic review of needling therapies in the management of MTrP pain. Marked improvements occurred in all groups in which trigger points were directly needled, but the authors concluded that the hypothesis that needling therapies have efficacy beyond placebo is neither supported nor refuted by the evidence from clinical trials. A recent systematic review [68] identified 26-randomized control trials of AcP and dry needling in the management of MTrP pain after searching electronic database. Only seven studies were included, but needling was not found to be significantly superior to

placebo after a meta-analysis. They have concluded that there is limited evidence deriving from one study that deep needling directly into MTrPs has an overall treatment effect when compared with standardized care. They have also suggested that the limited sample size and poor quality of these studies highlight and support the need for large scale, good quality placebo controlled trials in this area.

Objective evaluation of the effectiveness of trigger point acupuncture on pain and quality of life in chronic neck pain patients compared to three other AcP treatments (acupoints, nontrigger point and sham treatment) was conducted by Itoh and his colleagues [69]. They found that the trigger point AcP group reported less pain intensity and improved quality of life compared to the sham or nontrigger point groups after treatment, and suggested that trigger point AcP therapy might be more effective on chronic neck pain in aged patients than the standard AcP therapy. In a more recent study, Sun et al. [70] investigated the effects of AcP on patients with chronic neck myofascial pain syndrome by a single-blind randomized controlled trial and found that AcP group had greater improvement in physical functioning and role emotional of Short Form-36 quality of life than the control group at 12 weeks followup.

5.2. Basic Researches of Dry Needling for MTrPs. It has been suggested that LTR should be elicited during dry needling in treating MTrPs [65, 71]. An animal model for myofascial pain study was initially reported in 1994 [71]. A sensitive spot could be found in the biceps femoris muscle of a rabbit, which defined as a "myofascial trigger spot (MTrS)". When this sensitive spot was compressed before anesthesia, the rabbit screamed and kicked with an expression as if suffering very painful stimuli. This spot was marked and the animal was anesthetized for further study. This rabbit MTrS model provided at least three important characteristics similar to human MTrP: pain, LTR, and spontaneous electrical activity (SEA) and can be reasonably accepted for scientific research [71]. Local twitch response, a sudden brisk powerful contraction of a group of muscle fibers, could be elicited by needle stimuli in the MTrS [71]. Both LTR and SEA were suppressed after repeated needling on the same locus in the rabbit MTrS region [72]. It appears that, after a sensitive locus is encountered, and an LTR is elicited, the irritability of this sensitive locus (nociceptors) can be suppressed.

It has been suggested that LTR is an involuntary spinal reflex contraction of muscle fibers within a taut band, and occurs during needling of a taut band associated with pain relief and reduction of stiffness [73]. Shah and his colleagues [74, 75] developed a microanalytical system, including a small size and shape needle (as an AcP needle) to simultaneous sampling of skeletal muscle tissue to analysis the biochemical milieu of substances related to pain and inflammation. They found the concentrations of substance P (SP), calcitonin gene-related peptide (CGRP), bradykinin (BK), 5-hydroxytryptamin/serotonin (5-HT), norepinephrine (NE), tumor necrosis factor alpha (TNF-α), and Interleukin 1-beta (IL 1-β) were higher in the active MTrP group than in the latent MTrP and no-MTrP groups before elicited LTR. In the active MTrP group, the SP and CGRP concentrations post-LTR, corresponding to clinically observed decrease in pain and tenderness after MTrP release by dry needling were significantly lower than the pre-LTR values with compared in the latent MTrP and no-MTrP groups.

5.3. Probable Mechanism of Dry Needling for MTrPs. The most likely mechanism of pain relief by needle stimulation is hyperstimulation analgesia [76] via the descending pain inhibitory system. Melzack's gate control theory of pain describes the modulation of sensory nerve impulses by inhibitory mechanisms in the central nervous system [76]. The strong pressure stimulation to the MTrP loci can provide very strong neural impulses to the dorsal horn cells in the spinal cord, which may then break the vicious cycle of the MTrP circuit [2, 8]. The fast needle movement technique developed by Hong [21] can provide high-pressure stimulation, then inactive the MTrPs [5, 77]. Effective inactivation of the MTrP can relieve the pain and uncomfortable symptom [2, 10, 22, 65, 66]. The mechanism of local effects on the site (MTrP) of needling for the immediate relief of pain after AcP or dry needling has been consider to be mediated via the neural pathway [27, 77].

Gerwin et al. [78] claimed that the muscle soreness and pain associated with MPS is related to the chemical activation of nociceptors by substances released from surrounding injured tissue, then stimulate a unique cascade of cytokines that are integral to the inflammatory response. There is a biochemical basis to the development of peripheral and central sensitization in muscle pain while AcP (or dry needling) to the MTrP. In recent Shah's researches [74, 75], they confirmed that biochemicals associated with pain, inflammation, and intercellular signaling (e.g., inflammatory mediators, neuropeptides, catecholamines, and cytokines) were elevated near the active MTrPs differentiated from latent MTrPs and muscle without MTrPs. Assaying the peripheral milieu of a MTrP before, during, and after an LTR could disclose changes in bioactive substances that may contribute to myofascial pain. These initial peripheral conditions within muscle seem to be the source of feed-forward mechanisms that transform and intensify central processing of muscle pain.

6. Clinical Studies of Remote Needling (Including Acupuncture) for MTrP

6.1. Selection of Acupoints Based on TCM Principles. AcP on the tender points has been commonly used as a treatment for chronic musculoskeletal pain and appears to alleviate pain and stiffness in clinical practice. These tender points are known to be located at traditional acupoints, "*Ah-Shi*" points. They are supposed to be the sites where nociceptors and polymodal receptors, could be sensitized by various factors. Thus, AcP on the tender points may activate sensitized polymodal receptors and result in stronger effects on pain relief [79]. But, AcP is not only applied to the "*Ah-Shi* " point but also to the distal acupoints for the treatment of chronic pain.

In the view of TCM, the Huang di nei jing (Yellow Emperor's Inner Canon) [36, 37] states that, "if someone has disease related with the left side, the treatment point is the right side, and vice versa,"emphasizing the importance of treatment side. In Han's review article, he suggested that there seem to be at least three principles for selection of acupoints based on the TCM principles. (a) "It is more important to identify the right meridian rather than the right point within the meridian". (b) "To use the meridian with its pathway reaching the vicinity of the diseased organ" (c) "Where there is pain, there is a transport point" ("*Ah-Shi*" point) [41].

Cheng [80] reviewed the AcP treatment formulae for some common conditions and found that the acupoints traditionally used for the treatment have a neuroanatomical significance from the viewpoint of Western medicine in many cases. These mechanisms of action include intramuscular stimulation for treating muscular pain and nerve stimulation for treating neuropathies. In Cheng's later study [81], he examined the relationship between the anatomical location of traditional acupoints and their clinical indications as stated in two textbooks of TCM and concluded that (1) the acupoints in the trunk and their stated effects on the internal organs in the trunk have a segmental relationship, (2) the acupoints in the trunk and extremities have a musculoskeletal effect that is local or regional, but not distal, and (3) the acupoints on the head and neck preferentially affect the nearest organ.

6.2. Effectiveness of Needling at Distant Points for MTrP. Some clinical trial studies showing that AcP's analgesic effect can reach distant sites in the recent research. Irnich and his colleagues evaluated immediate effects of needle AcP at distant points and dry needling of local MTrPs on motion-related pain and cervical spine mobility in chronic neck pain patients compared to a sham laser AcP. Their results indicated that AcP has specific effects on motion-related pain and range of motion in patients with chronic neck pain. Needling at distant points improving range of motion more than at local points, and local points seeming ineffective to obtain immediate relief of motion-related pain [82]. Xue et al. conducted a randomized, single-blinded, sham-controlled, crossover clinical trial to investigate the efficacy of EAcP, applied to distal acupoints only, for tension-type headache and found it is effective for short-term symptomatic relief of tension-type headache [83].

Hsieh and her colleagues [73] conducted a clinical study and provided evidence that dry needling-evoked inactivation of a primary (key) MTrP (in the infraspinatus muscle) inhibits the activity in satellite MTrPs (in the ipsilateral anterior deltoid and extensor carpi radialis longus muscles) situated in its referral pain zone. In the recent study of Tsai et al. [84], they found dry needling of a distal MTrP (in the extensor carpi radialis longus muscle) could provide a remote effect to reduce the irritability of a proximal MTrP (in the upper trapezius muscle). Matsubara and her colleagues [85] had investigated the effect of acupressure at local and distal acupoints in females with chronic neck pain, and found pain-related condition (like verbal rating scale, neck disability index, State-Trait anxiety inventory, and muscle hardness) improved not only the local points but also the distal acupoints with compared with control group.

The clinical implications of these above studies may involve the selection of remote acupoints for treating MPS patients, which is thought to be one of the key issues in therapeutic effectiveness of AcP. But the selective outcome assessments in these researches are all subjective, like verbal rating scale and questionnaire, and some semisubjective, like pain pressure threshold obtained via algometer. Some objective assessment is needed.

6.3. Correlation between Acupoints and MTrPs. Important characteristics of an MTrP include local pain or tenderness, referred pain or referred tenderness, and local twitch response. Melzack et al. [86] published the first review article in discussion with correlations and implication between trigger point and acupoints for pain. He found the trigger points are firmly anchored in the anatomy of the neural and muscular systems, while acupoints are associated with an ancient conceptual but anatomically nonexistent system of meridians. He suggested a hypothesis that trigger points and acupoints for pain, though discovered independently and labeled differently, represent the same phenomenon and concluded a remarkably high degree (71%) of correspondence with MTrPs and acupoints [86]. Hong had concluded that there are many similarities between acupoints and MTrPs including their location and distribution, pain and referred pain patterns, local twitch responses (*De-Qi*), and so forth [77].

Travell and Simons [1] said: "acupuncture points and trigger points are derived from vastly different concepts. The fact that a number of pain points overlap does not change that basic difference. The two terms should not be used interchangeably". Birch [87] revisited trigger point-AcP point correlations through a more extensive examination of the AcP literature. He claimed that the findings of Melzack's 1977 study appear to be incorrect, 71% correspondence of trigger points to acupoints is conceptually not possible. He suggested that some overlap in the location of acupoints and trigger points is possible, but unlikely to be more than chance (not more than 40%, probably closer to 18%), and such similarity of location does not imply a correlation [87]. Beside, Birch found trigger points are a much better match to the class of acupoints called "*Ah-shi*" points than to the "channel" and "extra" acupoints in the treatment of pain and approximately 35% of recommended acupoints in the treatment of pain are distant from the site of the pain [87].

Dorsher [88] comprehensively examined the anatomic and clinical relationships between each trigger point described by Travell and Simons [1, 89] and the classical, "miscellaneous," and "new" acupoints described by the Shanghai College of Traditional Medicine [90]. A total of 255 trigger points were compared with 747 acupoints. He found strong anatomic (92%), clinical (79.5%), and meridian-referred pain (76%) correspondences of trigger and acupoints in this study and suggested AcP meridians were shown not only to exist conceptually but also, to be

physiologic (and possibly anatomic) entities. In the later study, Dorsher [91] reviewed AcP references and literature to re-examine the validity of the findings by Birch in 2003 [87]. He suggested the conceptual comparison of trigger points to classical acupoints in pain disorders treatment, and their clinical correspondence in this regard is likely 95% or higher. The AcP and myofascial pain traditions have fundamental clinical similarities in the treatment of pain disorders and myofascial pain data and research may help elucidate the mechanisms of AcP's effects [91].

6.4. Objective Assessment for the Remote Effect of Dry Needling (Acupuncture) for MTrP. SEA, include EPN and endplate spike are usually observed in an MTrP region in human. The prevalence of EPN [92] or the amplitude of EPN [35] is proportionate to the irritability of a MTrP. Current evidence shows that SEA at MTrP originates from the extrafusal motor endplate [93], and Ge et al. [94] concluded that SEA at MTPs might play a significant role in the induction of pain.

In the recent studies of Chou et al. [95], they chose the changes of mean EPN amplitude for the objective outcome assessment and found the MTrP irritability in the upper trapezius muscle could be suppressed after a remote AcP treatment on both *Wai-guan* and *Qu-chi* acupoints. Beside, needling to the remote acupoints with multiple needle insertions of modified AcP technique seems better than simple needling insertion and sham AcP.

7. Animal Studies of Remote Needling (Including Acupuncture) for MTrP

Referred tenderness is a phenomenon of remote referral of pain in response to compression of an MTrP, while referred pain is spontaneous pain referred to the remote sites from an MTrP [5]. The occurrence of referred tenderness and/or pain depends on the irritability of the MTrP and the pressure of compression [3, 96, 97]. For the MTrP in a certain muscle, the referral pain area locates within the same territory consistently if it is elicited at different time on the same person or at any time in different persons [1, 89].

In those previous researches, Mense et al. have demonstrated the referred pain from a muscle to another distant muscle in animal studies [98–100]. Pain signals from peripheral stimuli could be electrophysiologically recorded from sensory neurons in the dorsal horn of the spinal cord in a rat. For a dorsal horn neuron, mapping various sites receiving stimuli to elicit responses of this dorsal horn neuron can identify its receptive field. Later, Mense and Simons [101] conducted an animal study on the referred pain from a muscle to other distant ones. They suggested that strong noxious stimulus could send the impulse to and induce the corresponding dorsal horn neuron release substance P and calcitonin gene-related peptide (CGRP). Then increase the efficacy of silent synaptic connections as a consequence of central sensitization in the spinal cord level.

Sluka and colleagues [102] developed a model of musculosckeletal pain. Repeated injection of low pH saline into the gastronemius muscle and a long lasting, widespread mechanical hyperalgesia without motor deficits was produced. Contralateral decrease in mechanical threshold was noted and suggested centrally mediated hyperalgesia. In Sato's recent studies [103] of the neural mechanisms of the reflex effects on visceral functions of AcP-like stimulation applied to the skin and underlying muscle by twisting a needle in anesthetized rats, they have identified a wide variety of reflex responses in remote modification of various organ functions.

Hsieh's more recent study [104] is the first animal study to investigate the nueral mechanism of the remote effects of dry needling. As demonstrated in their study, the irritability of MTrSs at biceps femoris muscle (proximal MTrS) could be modulated by the remote effect of dry needling either ipsilaterally or contralaterally at MTrS of gastrocnemius muscle (distant MTrSs). After the transection at either ipsilateral tibial nerve or L5-L6 segments, loss of this remote effect on the change of EPN amplitude at MTrS of biceps femoris muscle was note, but not at T1-T2 segments. They have found that the neural pathway of the remote needling effect is mediated via an intact afferent connection from the site of stimulation to the spinal cord and a normal spinal cord function at the level corresponding to the innervations of the responded remote muscle. They further suggested that the influences from higher supraspinal level such brainstem, midbrain structures involved in the descending pain inhibitory system needs further investigation.

8. Possible Mechanism for Remote Needling (Including Acupuncture) of MTrP

The descending pain inhibitory system [38, 105–107] is probably involved in the mechanism of immediate pain relief due to needling (including acupuncture). Either hyperstimulation analgesia for general pain control [76] or disruption of "MTrP" circuit for myofascial pain control [2, 8, 104] as a proposed mechanism of needling effect for pain relief is actually via the descending inhibitory system.

A low-pressure stimulation to a sensitive locus may elicit a local pain only. When the stimulation force is increased progressively, the subject who has been needled may feel increased of pain intensity, and then may feel referred pain, and finally LTR can be elicited. Immediate relief of MTrP pain can be expected if LTRs are elicited during needling of the MTrP [21, 65, 108, 109], and the irritability of this sensitive locus can be suppressed [35, 92]. When a LTR is elicited, the patient usually feels a sharp pain with referred pain and muscle twitching. Such feeling is similar to that when a "*De-Qi*" effect is obtained during AcP therapy.

Regarding the mechanism of remote needling (AcP) effects to inactivate an MTrP, it is probably related to a spinal cord mechanism similar to the MTrP mechanism [3, 77]. It is possible that activation of nociceptors in the skin or muscles by needle stimulation (high pressure) can send strong sensory impulses to the spinal cord or higher center to interfere with all the related "neural circuits" of pain modulation (similar to "MTrP circuits" described by Hong) [2, 8]. Furthermore, AcP (needling) to a key MTrP can also

inhibit the irritability of satellite MTrPs [73] due to central desensitization phenomenon.

In Cheng's study [81], he concluded acupoints within certain spinal segments in the trunk affect the functioning of the organs that receive autonomic innervations from the same spinal segments. This is consistent with the concept of segmental AcP and the idea that AcP may act via the somatic sympathetic reflex with a spinal pathway to affect the trunk organs. Hsieh et al. [104] suggested that an intact afferent nerve from the remote stimulation site and normal spinal cord segments corresponding to the innervation of the affected proximal muscle are essential for the remote effect from either ipsilateral or contralateral needling stimulation. This neural pathway of remote effectiveness is probably mediated via a spinal reflex similar to that mediated the LTR [71, 110] and probably also similar to that for the referred pain. The physiological basis for the remote effects of AcP therapy may relate to a consequence of diffuse noxious inhibitory control that induced by noxious stimulation applied at the painful region (such as trigger point needling) or at a remote site (such as in remote AcP or dry needling) [111, 112].

9. Conclusion

Myofascial pain is one of the most common problems of musculoskeletal pain and is treated with a variety of conservative and invasive therapies. Previous clinical and animal investigations on the MTrP treatments focused on the existence of taut band, LTR, and referral pain. Tender points or MTrPs as "*Ah-Shi*" points are frequently used in AcP for MPS pain control. Recently, remote effectiveness of AcP (or dry needling) has been emphasized.

Although the specific pathophysiological basis of MTrP development is still not completely clear, several promising scientific studies (i.e., electrophysiological, neurophysiological, and biochemical) have revealed objective abnormalities. These findings suggest that myofascial pain is a complex form of neuromuscular dysfunction consisting of motor and sensory abnormalities involving both the peripheral and central nervous systems, and needling therapy can provide significant pain relief via neural mechanism.

Disclosure

Financial disclosure statements have been obtained, and no conflict of interests have been reported by the authors or by any individuals in control of the content of this paper.

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Research Article

Remote Subcutaneous Needling to Suppress the Irritability of Myofascial Trigger Spots: An Experimental Study in Rabbits

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Objective. To obtain electrophysiological effects of Fu's subcutaneous needling (FSN) on needling distance by assessment of endplate noise (EPN) recorded from the myofascial trigger spots (MTrSs) in rabbit skeletal muscle. *Method*. Eighteen New Zealand rabbits weighing 2.5–3.0 kg were randomly divided into two groups as follows: proximal needling (PN) group and distal needling (DN) group. The needling procedure followed the instructions described by the inventor of FSN, including needling insertion and swaying movement. The amplitudes of EPN on the MTrS region of BF muscle were recorded as an index of MTrS irritability. Random sampling of EPN tracings were taken for further analyses before, during, and after FSN treatment. *Results*. In PN and DN groups, the trends of EPN amplitude alterations were similar at conditions before, during, and after FSN treatment. The degree of reduction in the EPN amplitude in PN group was significantly higher than that in DN group. There were no significant changes in EPN amplitudes in the MTrS of contralateral BF without FSN intervention either in DN or PN group. *Conclusion*. The irritability of proximal MTrSs could be modulated after ipsilateral FSNs. The placement of FSN may affect the effectiveness of suppression of irritability of MTrSs.

1. Introduction

Myofascial trigger point (MTrP) is the most tender (hyperirritable) spot in a taut band of skeletal muscle fibers, characterized by a specific pattern of referred pain and local twitch responses (LTR) [1, 2]. Based on the studies on both human and animal subjects, it has been demonstrated that there are multiple sensitive loci in an MTrP region [3, 4]. These sensitive loci are probably nociceptors located in the endplate zone [5]. The prevalence of endplate noise (EPN), as recorded by an electromyographic (EMG) equipment, is significantly higher in an MTrP region than in a non-MTrP region [6, 7] and is highly correlated with the irritability (sensitivity) of an MTrP [8]. Recently, it has also been found that the changes in EPN amplitude significantly correlated with the changes in MTrP irritability [9, 10]. Therefore, MTrP irritability can be objectively assessed with the prevalence or amplitude changes of EPN that are recorded in the MTrP region. The advantage of the amplitude changes of EPN could be the real time recording the alternations of MTrP irritability, that the prevalence of EPN could not obtain. An animal model of MTrP has been established since 1994 [3] for various studies [11–15]. The rabbit myofascial trigger spot (MTrS) is similar to human MTrP in many aspects. EPN can also be recorded from MTrS and can be used for the assessment of therapeutic effectiveness of various modalities [16–18].

Needling therapy includes any treatment with one or more needles. The needle used for medical treatment can be purely a solid metal rod with a sharp tip such as traditional

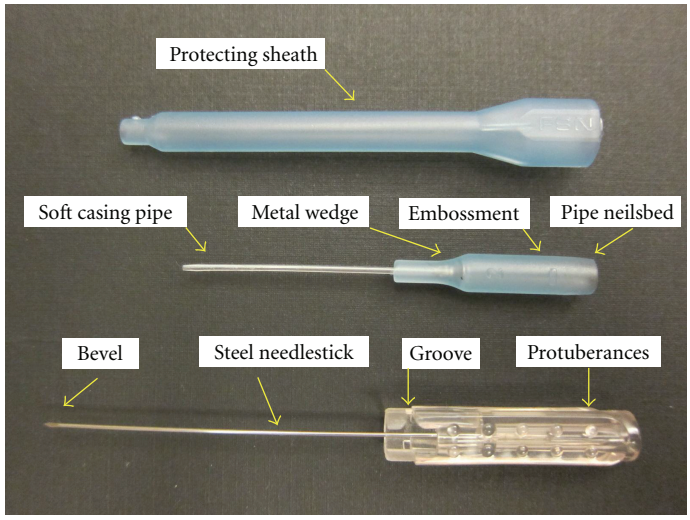


Figure 1: Three parts of Fu's subcutaneous needling.

acupuncture needle or can be specifically made with a central hollow as a pathway of drug for injection such as a regular injection needle used in general medical practice. "Dry needling" is a pure penetration of a needle through the skin without introduction of any drug. For dry needling, the site of treatment can be at the site of pain (direct dry needling) or far from the site of pain (remote dry needling). Either direct dry needling or remote dry needling, the following techniques can be used: traditional acupuncture [19–27], dry needling with multiple rapid insertions [9, 10, 28–34], and dry needling with electrical stimulation (similar to electrical acupuncture) [35–37]. However, superficial dry needling [38, 39] and deep dry needling for soft tissue release are usually performed directly over the painful lesions only, and Fu's subcutaneous needling [40–42] is usually applied over the remote non-painful site only.

Fu's subcutaneous needling (FSN), one type of remote subcutaneous needling, is a therapeutic approach mainly for musculoskeletal painful disorders. This procedure is performed by inserting a special trocar needle (Figure 1) into the subcutaneous layer around the afflicted spot to achieve the desired effect. In English, it was first described in the article by Fu and Xu in the journal of "The Pain Clinic" [40]. Since then, a series of research papers have been reported and claimed the clinical effectiveness, including painful diseases [43], lower back pain [41], and MTrP in the neck [42]. The way of manipulation of FSN is different from traditional acupuncture and other needling approaches. The FSN is inserted into non-diseased areas based on the nature of trigger points and the needle placement is restricted to the subcutaneous tissue (Figure 2(a)); the tip of FSN is directed to the painful region. Specifically, FSN should be swayed from side to side (Figure 2(b)) and may be retained in the subcutaneous tissues for a prolonged period of time to obtain a curative effect [40, 44].

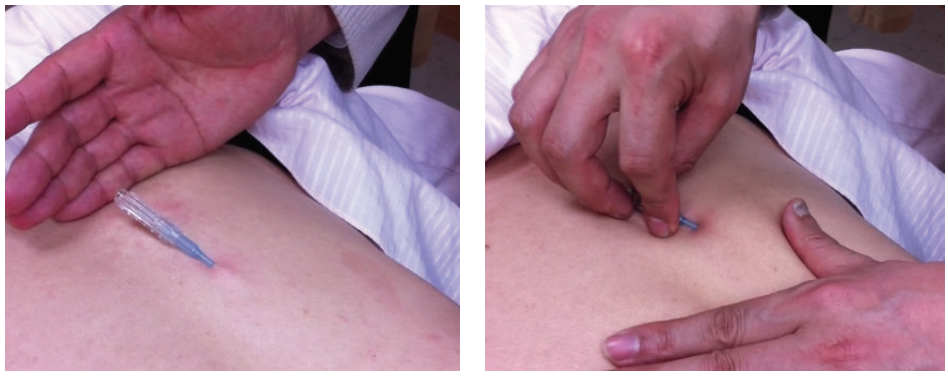
Although many clinical evidences of FSN have been reported as mentioned above, its underlying mechanism is still unclear and needs to be further investigated by using the animal study. In this study, we aim to obtain electrophysiological confirmation of the remote effect of FSN and compare the effectiveness of needling sites with different distance from the painful site based on the assessment of EPN recorded from the MTrSs in rabbit skeletal muscle.

2. Materials and Methods

2.1. General Design. The FSN-induced EPN alterations on the MTrS irritability (assessed with EPN amplitude changes in the electromyographic recordings) at bilateral biceps femoris (BF) muscle were examined. A total of 18 rabbits were randomly divided into 2 groups based on the placement of FSN (Figure 3): on subcutaneous layer over the insertion region of the BF muscle (proximal needling, PN group, $n = 9$, Figure 4) and on subcutaneous layer over the insertion region of the gastrocnemius muscle (distal needling, DN group, $n = 9$, Figure 4). The FSN treatment side of animal's hindlimb was randomly selected by manipulators. FSN treatments were repeated for two times (Dur1 and Dur2) with an interval of two minutes between the two needling therapies. Continuous tracings of EPN were recorded from BF muscle before (Pre-), during the 1st needling (Dur1-), after the 1st needling (Post1-), during the 2nd needling (Dur2-), and after the 2nd needling (Post2-) of FSN in anesthetized animals (Figure 5).

The changes in MTrS irritability (EPN amplitude) in PN and DN groups were compared for all EPN recoding periods including Pre-, Dur1-, Post1-, Dur2-, and Post2-FSN conditions.

2.2. Animals Care and Preparation. The experiments were performed on adult New Zealand rabbits (body weight 2.5–3.0 kg). Each animal was housed individually in a standard polycarbonate tub cage lined with wood chip beddings and had free access to food and water. The cage was placed in an air-conditioned room (25 ± 1°C), with noise level less than



(a) (b)

Figure 2: (a) The Fu's subcutaneous needling (FSN) is placed to the subcutaneous tissue, and (b) swayed during treatment.

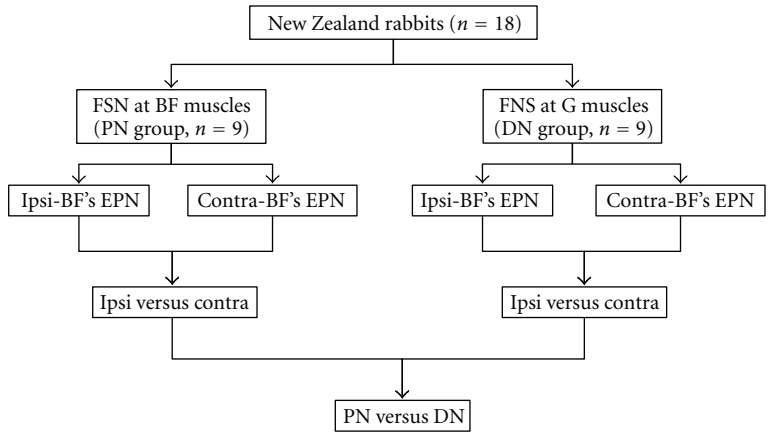


Figure 3: Flow chart for the animal study. (BF = bicep femoris; Contra = EPN recording side contralaterally to FSN side; DN = distal needling; EPN = endplate noise; FSN = Fu's subcutaneous needling; G = gastrocnemius; Ipsi = EPN recording side ipsilaterally to FSN side; PN = proximal needling).

40 dBA and a 12-hour alternating light-dark cycle (6 : 00 am to 6 : 00 pm). The ethical guidelines of the International Association for Study of Pain in animals were followed [45]. All animal experiments were conducted with procedures approved by the Animal Care and Use Committee of a university in accordance with the Guidelines for Animal Experimentation.

Before anesthesia, the most tender spots (i.e., MTrS) of BF muscle were identified by finger pinch. The animal's reactions to the pinch stimulation were observed (withdrawal of the lower limb, turning its head, screaming, etc.) to confirm the exact location of an MTrS. The painful region was marked on the skin with an indelible marker for electrophysiological assessment. Then the animals were anesthetized with 2% isoflurane (AErrane, Baxter Healthcare of Puerto Rico, PR, USA) in oxygen flow for induction followed by a 0.5% maintenance dose [46]. Body temperature, monitored by the thermistor probe of a thermometer (Physiotemp Instrument, Clifton, NJ, USA) in the rectum, was maintained at approximately 37.5°C using a body temperature control system consisting of thermostatically regulated DC current heating pad and an infrared lamp. The hindlimbs of anesthetized rabbits were shaved and cleaned with povidone-iodine solution. The skin of the lateral thigh in one randomly selected side was incised to expose the BF muscle, which were served as an EPN recording site. The marked spots in the BF muscle were grasped between two fingers from behind the muscle and the muscle is palpated by gently rubbing (rolling) it between the fingers to find a taut band. A taut band feels like a clearly delineated "rope" of muscle fibers and is roughly 2-3 mm or more in diameter. The fibers of the taut band are unmistakably firmer in consistency than the surrounding muscle.

2.3. Fu's Subcutaneous Needling Manipulation. The FSN manipulation procedure was followed the instructions described by the inventor of FSN, including needling insertion and swaying movement [40, 41]. Step 1: quickly penetrate the needle obliquely through the skin. The angle between the needle and skin is about 20°–30°. Make sure the needle tip is not too deep and stop when the needle tip just touches the muscle layer. Step 2: draw back the needle a little to the subcutaneous layer. Step 3: push forward the needle parallel to the skin surface (maintaining in the subcutaneous layer)

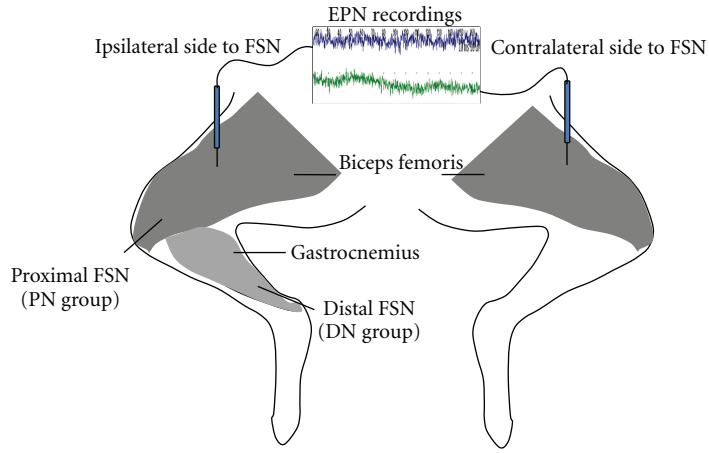


Figure 4: The sites and sides of endplate noise (EPN) recordings, and that for Fu's subcutaneous needling (FSN) for animals in proximal needling (PN) and distal needling (DN) groups.

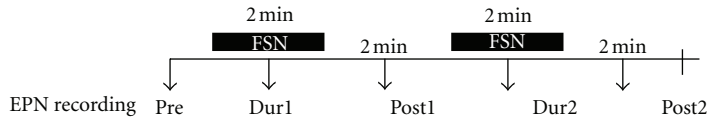


Figure 5: Sequences of Fu's subcutaneous needling (FSN) and endplate noise (EPN) assessment in the whole course of the experiment.

until the whole soft tube is under the skin and leave the needle in the subcutaneous layer. Step 4: draw the steel needle back 3 millimeters to make the steel tip wrapped in the soft tube, then sway the needle smoothly and rhythmically from one side to another horizontally at a rate about 200 times in 2 minutes. During the swaying movement, the needle remained in the subcutaneous layer (Figure 2). The same investigator performed all needling procedures for all rabbits.

2.4. Recording of Endplate Noise (EPN)

2.4.1. Electromyography Setting. For EPN assessment, a two-channel digital EMG machine (Neuro-EMG-Micro, Neurosoft, Ivanovo, Russia) and monopolar needle electrodes (37-mm, disposable, Teflon-coated, model 902-DMF37-TP; VIASYS/Cardinal Healthcare, Dublin, OH, USA) were used. The gain was set at 20 μV per division for recordings from both channels. Low-cut frequency filter was set at 100 Hz and the high-cut at 1,000 Hz. Sweep speed was 10 ms per division. The search needle for EPN recording was inserted into the MTrS region and was connected to the 1st channel of the EMG machine. The control needle was inserted into the non-taut band region near the MTrS in the same muscle and was connected to the 2nd channel. A common reference needle electrode for each channel was placed on the incised skin and connected to both channels via a y-connector.

2.4.2. Search for Endplate Noise. An investigator who was blind to the group assignment performed this procedure. The search needle was inserted into the MTrS region in a direction parallel to the muscle fibers at an angle of approximately 60° to the surface of the muscle. After initial insertion just short of the depth of the MTrS or to comparable depth in the case of control sites, the needle was advanced very slowly. Each advance was of minimal distance (about 1 mm). When the needle approached an active locus (EPN locus), the continuous distant electrical activity, that is, EPN, can be heard. A site was an active locus when EPN was identified if (1) EPN-like potentials persisted continuously for more than 300 msec, (2) the potentials had an amplitude of >10 μV (which was more than twice the instrumentation noise level of 4 μV that was observed in control recordings taken at the beginning and at completion of each track), and (3) the adjacent control channel was not recording potentials greater than the instrumentation noise level. As soon as the EMG activity (EPN) with an amplitude higher than 10 μV could be recorded, the examiner stopped to move and remain the needle there to ensure that this EPN could run continuously on the recording screen with constant amplitudes. Then, continuous EPN tracing was recorded throughout the whole course of FSN treatment and provided the opportunity for continuous visual observation of EPN changes on the EMG screen. The whole EPN tracing found in MTrS of BF muscle were recorded for the analysis of amplitude changes.

2.4.3. Measurement of the Amplitude of Endplate Noise. Randomly selected five samples of EPN recordings (50 msec for each) were taken before (Pre-), during (DN-) and after (Post-) the FNS treatment for both groups. The mean amplitude of EPN was analyzed and calculated using embedded software in the Neuro-EMG-Micro equipment.

Table 1: The serial alterations of EPN amplitudes (μV) in proximal and distal manipulation of Fu's subcutaneous needling (FSN).

Condition	PN group		DN group	
	Ipsi	Contra	Ipsi	Contra
Pre	5.80 ± 0.60	4.88 ± 0.80	5.79 ± 0.61	4.88 ± 0.35
Dur1	6.97 ± 0.47	4.84 ± 0.50	6.76 ± 0.89	4.85 ± 0.41
Post1	5.37 ± 0.63	4.82 ± 0.46	5.44 ± 0.76	4.82 ± 0.64
Dur2	5.76 ± 0.88	4.76 ± 0.79	5.68 ± 0.82	4.75 ± 0.53
Post2	4.52 ± 0.76*	4.80 ± 0.43	4.73 ± 0.74*	4.78 ± 0.41
P value[a]	0.001	1.00	0.006	1.00
poc hoc test[b]	*Dur1 versus Post2		*Dur1 versus Post2	

[a]Tested by ANOVA.
[b]Tested by Scheffe's method.
*Indicates significant difference ($P < 0.05$) tested by Scheffe's method.
Abbreviations: Contra: EPN recording side contralaterally to FSN side; DN: distal needling; EPN: endplate noise; Ipsi: EPN recording side ipsilaterally to FSN side; PN: proximal needling.

2.5. Date Analysis. Data were expressed as the mean ± standard error of the mean (SEM). The serial differences in EPN amplitude among Pre-, Dur-, and Post-FSN conditions in each group were carried out using an ANOVA followed by a Scheffe's post-hoc analysis. The alteration of EPN amplitude was calculated as follow: percentage of EPN alteration = ((data in Dur- or Post-FNS condition − data in Pre-FSN condition)/data in Pre-FSN condition)/100%. The differences of reduction percentage between EPN recording sides ispi- and contra-laterally to FSN side and between PN and DN groups in each recording side were tested by Student *t*-test. A *P* value of <0.05 was considered to be statistically significant. All data was analyzed using Statistical Package for the Social Sciences (SPSS, version 12.0) for Windows.

3. Results

3.1. Effects of FSN on Serial EPN Recordings. The serial alterations of the mean EPN amplitude of the ipsilateral and contralateral BF muscle in Pre- Dur1-, Post1-, Dur2-, and Post2-FNS conditions in PN and DN groups were demonstrated in Table 1 and Figure 6. In PN group, the mean EPN amplitudes recorded from MTrS of BF muscle ipsilaterally to FSN were significantly different among Pre- Dur1-, Post1-, Dur2-, and Post2-FNS conditions ($P = 0.001$). The significant reduction of EPN amplitudes was found in Post2-FSN ($P = 0.001$) condition when compared with those in Dur1-FSN condition. But the EPN amplitudes recorded from MTrS of BF muscle contralaterally to FSN were no significant differences among Pre- Dur1-, Post1-, Dur2-, and Post2-FNS conditions ($P > 0.05$).

The trend of EPN amplitude in DN group was similar to those in PN group regardless of EPN recording sides. There were significant differences among Pre-, Dur1-, Post1-, Dur2-, and Post2-FSN conditions in the DN group in ipsilateral EPN recording side ($P = 0.006$), but not found in contralateral recording side ($P > 0.05$). The significant reduction of EPN amplitudes in ipsilateral recording side was also found in Post2-FSN ($P = 0.008$) condition when compared with those in Dur1-FSN condition in DN group.

In the PN group, the percentages of EPN amplitude alteration of ipsialteral BF were significantly increased in Dur1- and Dur2-FSN levels, and then was significantly decreased to much lower level in Post1- and Post2-FSN levels when comparing with those data recorded from contralateral BF. In the DN group, the trend of percentage of EPN alteration was similar (Figure 7).

3.2. Distance Effect of Fu's Subcutaneous Needling. After the whole course of treatments, the percentages of EPN amplitude alterations reduced significantly ($P < 0.05$) in the ipsilateral PN and DN groups. There were significant differences on the amount of reduction between PN and DN groups. The percentages of amplitude alterations were significantly reduced in the PN group when compared with those in the DN groups (Figure 6).

4. Discussion

4.1. Summary of Important Findings in This Study. To our knowledge, the present study is the first animal study to investigate the neural mechanism of the remote effects of FSN. In this study, we have found that the irritability of proximal MTrS at BF muscle could be modulated by the remote effect of FSN at ipsilateral distant leg. The placement of FSN (distance to the MTrS) may be a crucial factor on the suppressive effectiveness of irritability of MTrS.

4.2. Insertion Point and Needling Direction for Fu's Subcutaneous Needling. Fu's Subcutaneous Needling is a therapeutic approach mainly for musculoskeletal painful disorders, including myofascial pain syndrome. The choosing of insertion points and needle direction were based on Fu's experience and some rules in a famous ancient Chinese medical book (*Yellow Emperor's Internal Classic*) for pain syndromes (also called *Bi* syndromes) [41].

Some principles and clinical experiments of the locations and direction of the FSN insertion point(s) have been mentioned as followed: (1) the FSN needle does not reach the pain area, no matter how short the distance between needling

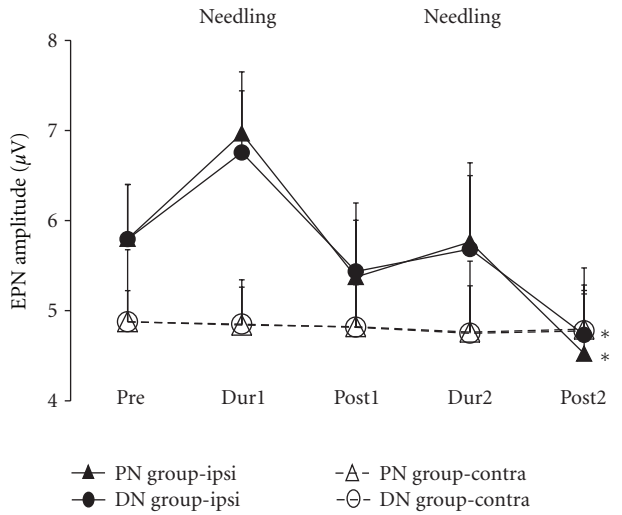


Figure 6: The serial changes of the mean amplitudes of endplate noise (EPN) in groups with proximal (PN group) and distal (DN group) Fu's subcutaneous needling (FSN). ipsi and contra indicate the EPN recording ipsilaterally and contralaterally to FSN. *Indicates $P < 0.05$ tested by ANOVA.

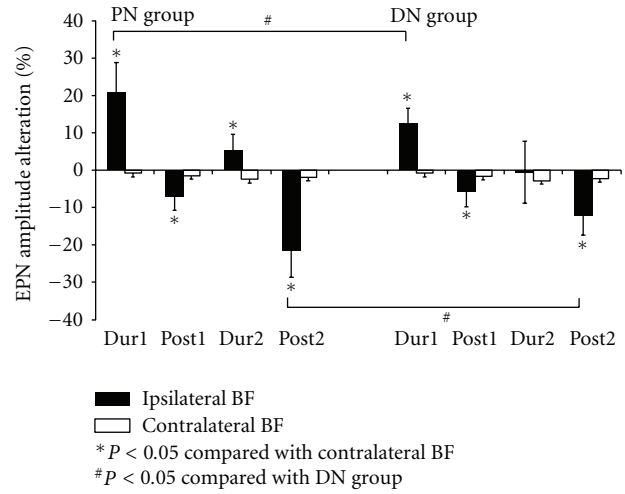


Figure 7: The percentages of EPN amplitude alteration in bilateral biceps femoris (BF) muscle in each condition when compared with the data before proximal and distal manipulation of Fu's subcutaneous needling (PN and DN group). Abbreviations: BF = biceps femoris; DN = distal needling; EPN = endplate noise; PN = proximal needling.

site and painful site [40]; (2) the distance should vary with individuals. For pain involving a large-area or for severe pain, the distance should be longer, and the insertion point is chosen near to the painful point if the painful area is small [40]; (3) needling directions are well correlated to the outcome [41].

4.3. Difference between Dry Needling (Acupuncture) and Fu's Subcutaneous Needling. Traditional acupuncture therapy is probably the oldest type of dry needling. The manipulation of the acupuncture needle is "fast in and fast out" or "rotation," but the FSN is moved from one side to another smoothly and rhythmically [41]. In regular acupuncture therapies, immediate pain relief can be obtained if the patient experiences "*De-qi*" reaction during therapy. The mechanism of local effects on the site of needling for the immediate relief of pain after acupuncture or dry needling has been consider to be mediated via the neural pathway [38, 47]. On the contrary, the FSN claims that the tip of the FSN needle had better not reach the painful spots [40], but good effectiveness could be obtained without "*De-qi*" or local twitch response. Fu and his colleagues [41] have hypothesized that no "*De-qi*" elicited during FSN maybe related to the paucity of free nerve endings and proprioceptive receptors in the subcutaneous layer.

4.4. Possible Mechanism of Fu's Subcutaneous Needling for Pain Control. The subcutaneous layer contains adipose tissue and connective tissue. Langevin and his colleagues [48] hypothesized that mechanical coupling between the needle and connective tissue with winding of tissue around the needle during needle rotation transmits a mechanical signal to connective tissue cells that may explain local and remote, as well as long-term effects of acupuncture. Fu and Xu [40] presumed that the mechanism of FSN probably acts on the mechanical forces of the subcutaneous layer by regulating the homeostasis of the connective tissue. At the later report, Fu and his colleagues [42] thought that there was little possibility that the nervous system could be involved in the action of FSN.

4.5. Possible Mechanism of the Remote Effect of Fu's Subcutaneous Needling. Although many clinical evidences of the remote influences of FSN have been reported [41–43], its underlying mechanism is still unclear and needs to be further investigated by using animal studies. The animal model with MTrS was well established previously [3, 18] and served in this study for further investigating the possible mechanism of remote effect after FSN. MTrP irritability can be objectively assessed with the prevalence or amplitude changes of EPN that are recorded in the MTrP region. It has been found that the changes in EPN amplitude significantly correlated with the changes in MTrP irritability in a recent study [9].

As demonstrated in previous study [15], the irritability of MTrS at BF muscle (proximal MTrS) could be modulated by the remote effect of dry needling ipsilaterally or contralaterally at MTrS of gastrocnemius muscle (distant MTrS). This remote effect depends on an intact afferent pathway from stimulating site to the spinal cord and a normal spinal cord function at the level corresponding to the innervations of the proximally affected muscle. However, the electrophysiological findings in this study demonstrated that FSN to MTrSs of distal muscles of ipsilateral gastrocnemius muscle could initially increase the irritability of MTrS in proximal muscle (BF), followed a suppression effect after cessation of needling, but not found in the contralateral side.

There weren't any contralateral remote effects found in this study. Therefore, it is very likely that the mechanism of FSN is not related to neural mechanism, but due to

the effect of mechanical connective tissue reaction as mentioned above. A direct mechanical connective tissue reaction cannot be transmitted to the other side of body. Similarly, the transmitting reaction of mechanical force is much stronger for the short-distance reaction than that of a longer distance. That is probably the reason why we obtained a stronger effect in PN than that in DN group.

4.6. Limitation of This Study. The most critical limitation of this study is the difficulty to confirm the correlation between the alterations of EPN amplitude and pain intensity in rabbit MTrS. We can confirm that in human study. Since there are many similarities between rabbit MTrS and human MTrP, we can reasonably assume that the amplitude of EPN recorded from a rabbit MTrS is related to the irritability of the MTrS similar to that in human MTrP. At least, our study could confirm that the FSN effect is not related to the psychological effect that previous author concerned [40]. It is also less likely that FSN effect is related to neural connection.

Lack of follow-up assessments for the long-term remote effect after the cessation of the FSN stimulation is another deficiency of this study. In addition, no placebo group (minimal/sham needling or other acupoint) was used in our study. It is obvious that great attention should be paid to all limiting factors discussed in this study. Further studies on the mechanical force effects based on a long-term follow-up of EPN amplitude after FSN treatments may be helpful for straightening out the deficiency of this study.

5. Conclusion

This study confirmed the electrophysiological phenomenon of the remote effect of FSN (one type of remote subcutaneous needling) and the possible pathway in response to this remote effect based on the assessment of EPN recorded for the MTrS in rabbit skeletal muscle which is equivalent to the MTrP in human muscle. It appears that the MTrS irritability can be suppressed after an ipsilateral remote FSN treatment, with a better effectiveness after the proximal FSN therapy than the distal one.

Author's Contributions

Y.-L. Hsieh had provided the same effort as Z.-H. Fu.

Disclosure

No commercial party having a direct financial interest in the results of the research supporting this paper has or will confer a benefit upon the authors or upon any organization with which the authors are associated.

Suppliers

(a) Neuro-EMG-Micro: Neurosoft, 5, Voronin Str, Ivanovo, Russia. (b) Statistical Package for the Social Sciences version 10.0 for Windows: SPSS Inc. Headquarters, 233 S. Wacker Dr, 11th Fl, Chicago, IL 60606.

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Research Article

Dry Needling at Myofascial Trigger Spots of Rabbit Skeletal Muscles Modulates the Biochemicals Associated with Pain, Inflammation, and Hypoxia

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Background and Purpose. Dry needling is an effective therapy for the treatment of pain associated with myofascial trigger point (MTrP). However, the biochemical effects of dry needling that are associated with pain, inflammation, and hypoxia are unclear. This study investigated the activities of β-endorphin, substance P, TNF-α, COX-2, HIF-1α, iNOS, and VEGF after different dosages of dry needling at the myofascial trigger spots (MTrSs) of a skeletal muscle in rabbit. Materials and Methods. Dry needling was performed either with one dosage (1D) or five dosages (5D) into the biceps femoris with MTrSs in New Zealand rabbits. Biceps femoris, serum, and dorsal root ganglion (DRG) were sampled immediately and 5 d after dry needling for β-endorphin, substance P, TNF-α, COX-2, HIF-1α, iNOS, and VEGF immunoassays. *Results*. The 1D treatment enhanced the β-endorphin levels in the biceps femoris and serum and reduced substance P in the biceps femoris and DRG. The 5D treatment reversed these effects and was accompanied by increase of TNF-α, COX-2, HIF-1α, iNOS, and VEGF production in the biceps femoris. Moreover, the higher levels of these biochemicals were still maintained 5 d after treatment. *Conclusion*. Dry needling at the MTrSs modulates various biochemicals associated with pain, inflammation, and hypoxia in a dose-dependent manner.

1. Introduction

Myofascial pain syndrome (MPS) is characterized by an acute or chronic regional muscle pain primarily caused by myofascial trigger points (MTrPs) located in taut muscle bands, fascia, or tendinous insertions [1–7]. The diagnosis of MPS is based on the identification of MTrPs in the taut band by palpation of tender nodules, local twitch response, and specific pain referral patterns associated with each MTrP [3, 7, 8].

To date, the neurophysiology and pathogenesis of MPS and MTrP have not been confirmed. Local compression by taut bands (muscle fibers that shorten in the absence of propagating action potentials) can impair arterial inflow and reduce the supply of oxygen, calcium, and other nutrients necessary for energy-dependent muscle relaxation and higher energy demands required by the aberrantly sustained muscle contraction [7]. Continued, persistent sarcomere contractures can distort and damage involved tissues, which may precipitate the synthesis and release of endogenous algogenic biochemicals and inflammatory substances that enhance nociception [3, 4, 9]. These effects suggest that persistent or chronic pain perception associated with MPS can involve numerous proinflammatory cytokines, neurotransmitters, and neuromodulators, including tumor necrosis factor-α (TNF-α), substance P, and cyclooxygenase-2 (COX-2), which relay pain signals from the peripheral to the central nervous system. An increase in β-endorphin level can suppress neurons from releasing substance P and thus,

inhibit pain transmission [10]. These observations, which provide biochemical evidence, correlated with recent, partially approved studies that demonstrated significantly higher concentrations of substance P and TNF-α in the local milieu of active MTrPs [9, 11]. Moreover, a number of hypoxic-responsive proteins, including hypoxia-inducible factor-1α, vascular endothelial growth factor (VEGF), and inducible isoform of nitric oxide synthases (iNOS), can be found in response to hypoxia and mechanical stimulation in skeletal muscles [12, 13].

Dry needling (i.e., without injectate) at MTrPs is an effective therapy that inactivates an MTrP if performed in a particular manner [14–18]. A systematic review of MPS treatment found that dry needling is as effective as lidocaine injections [18, 19]. However, other comparative studies reported on the negative effects of dry needling on the management of MTrPs [20]. These inconsistencies may have resulted from limited sample sizes, poor quality of placebo-controlled trials, and protocol (technique, particularly in eliciting local twitch responses (LTRs); dosage; and duration) of dry needling [4, 15, 18–20]. Therefore, the biochemical responses underlying the antinociceptive effects and pain relief associated with dry needling must be clarified to develop adequate treatment measures for MPS. To achieve this goal, the fluctuating levels of β-endorphin, substance P, TNF-α, COX-2, HIF-1α, iNOS, and VEGF at different dosages of dry needling at the myofascial trigger spots (MTrSs, similar to human MTrPs) of a skeletal muscle were assessed in the present study through a well-established rabbit model.

2. Materials and Methods

2.1. General Design. The fluctuating levels of biochemicals after dry needling to the rabbit biceps femoris containing MTrSs were examined. The MTrS of the biceps femoris muscle on a randomly selected side was treated with predetermined dosages of dry needling. A total of 80 rabbits were randomly and equally divided into four groups based on the dosages of dry needling: (1) the one-dosage dry needling (1D) group ($n = 20$) that received one session of dry needling, (2) the one dosage of sham dry needling (s1D) group ($n = 20$) that received one session of sham dry needling, (3) the five-dosage dry needling (5D) group ($n = 20$) that received five daily sessions of dry needling for five consecutive days, and (4) the five dosages of sham dry needling (s5D) group ($n = 20$) that received five daily session of sham dry needling. Half of the animals in each group were sacrificed on the day immediately after dry needling, and the remaining animals were sacrificed 5 d after dry needling for immunoassays and serology test (Figure 1). The immunoassays include the following: (1) β-endorphin, substance P, TNF-α, COX-2, HIF-1α, iNOS, and VEGF in the bicep femoris muscles containing MTrSs, (2) β-endorphin and substance P in the dorsal root ganglion (DRG) corresponding to the biceps femoris, and (3) TNF-α and β-endorphin in the serum. Individual serological tests for assessing serum β-endorphin and TNF-α levels were sampled before and after dry needling in five randomly selected animals from each group to avoid the effects of repetitive drawing on the results of immunoassays in the muscle and DRG. The flow diagram is presented in Figure 1.

2.2. Animal Care. Adult male New Zealand rabbits (ages 16 weeks to 20 weeks, body weight between 2.5 and 3.0 kg) were used in the experiments. The animals were housed individually in standard polycarbonate tub cages lined with a wood chip bedding and had unlimited access to food and water. The cages were placed in an air-conditioned room (25°C ± 1°C), with 40 dBA noise, and a 12 h alternating light-dark cycle (6:00 a.m. to 6:00 p.m.). Each animal was housed and cared for according to the ethical guidelines of the International Association for the Study of Pain in animals [21, 22]. Effort was made to minimize discomfort and reduce the number of animals used. All animal experiments were conducted by following the procedure approved by the Animal Care and Use Committee of a university in accordance with the Guidelines for Animal Experimentation. The general experimental conditions were essentially the same as those previously described [23–25].

2.3. Animal Model for a Myofascial Trigger Point Study. Hong and Torigoe [26] developed an animal model for an MTrP study on rabbits [26]. A specific hyperirritable spot (MTrS) in the rabbit biceps femoris muscle is similar to the human MTrP. LTRs can be elicited at this spot when the needle tip encounters a sensitive locus. Spontaneous electrical activities, including endplate noise and endplate spikes, can also be recorded frequently within this sensitive spot, similar to a human MTrP [27, 28]. This animal model has been used in numerous studies on myofascial pain [23–25, 27, 29, 30] and thus was deemed appropriate for the current study.

2.4. Identification of MTrS. Prior to administration of an anesthetic, the tenderest spots (i.e., MTrS) of the bicep femoris were identified by a finger pinch. The animal's reaction was observed (withdrawal of the lower limb, turning the head, screaming, etc.) to confirm the exact location of an MTrS. These painful regions were marked on the skin with an indelible marker. The animals were then anesthetized with 2% isoflurane (AErrane, Baxter Healthcare of Puerto Rico, PR, USA) in the oxygen flow for induction, followed by a 0.5% maintenance dose [31]. The body temperature was monitored by placing the thermistor probe of a thermometer (Physitemp Instruments, Inc., Clifton, NJ, USA) in the rectum. The temperature was maintained at approximately 37.5°C by using a body temperature control system consisting of a thermostatically regulated DC current heating pad and an infrared lamp. The biceps femoris of a marked hindlimb was grasped from behind the muscle, and the muscle was palpated by gently rubbing (rolling) it between the fingers to find a taut band. A taut band has the texture of a clearly delineated "rope" of muscle fibers and is roughly 2 mm to 3 mm or more in diameter. This area was designated for the dry needling treatment.

2.5. Dry Needling of the Biceps Femoris Muscle. All needling procedures were performed by the same investigator who

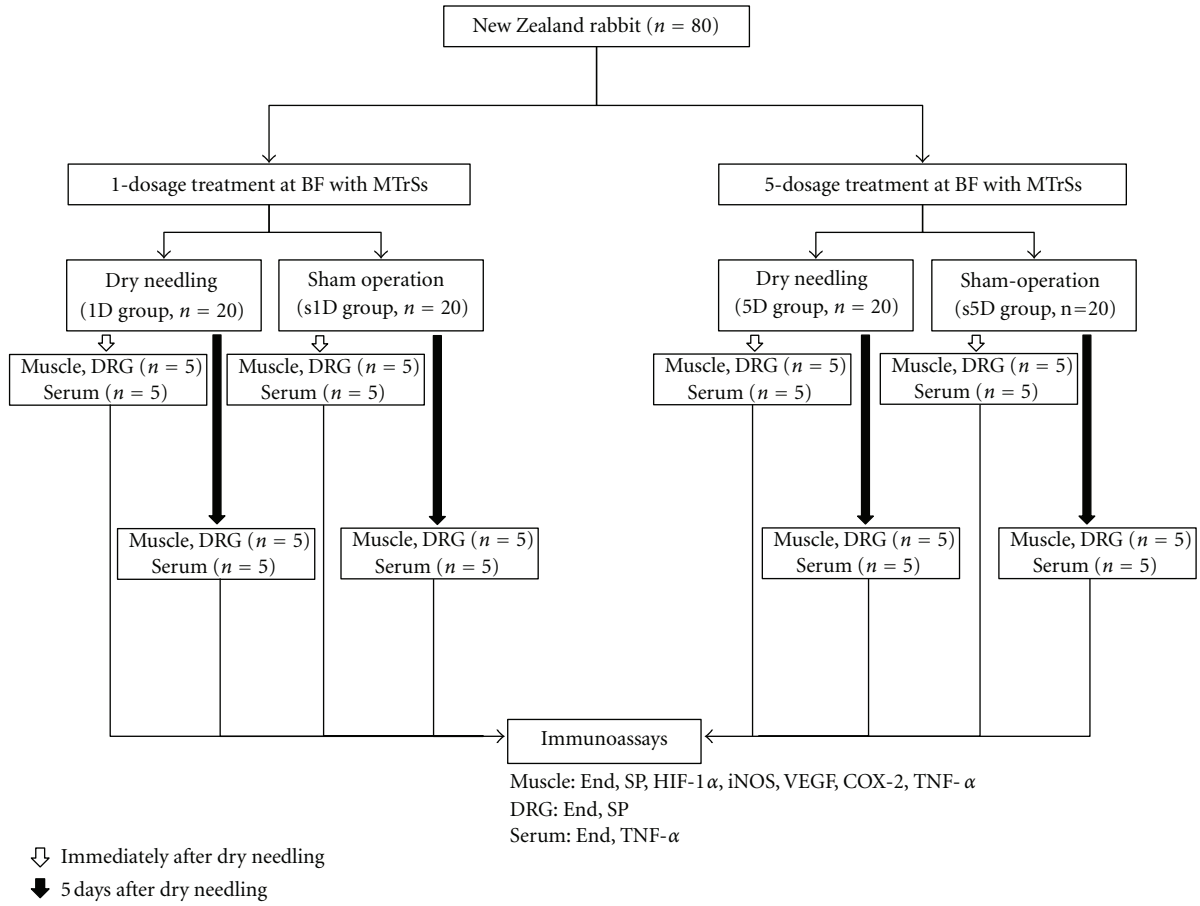


Figure 1: Flow chart for the animal study. Abbreviations: 1D, one-dosage dry needling; 5D, five-dosage dry needling; BF, biceps femoris; COX-2, cyclooxygenase-2; DRG, dorsal root ganglion; End, β-endorphin; HIF-1α, hypoxia-inducible factor-1α; iNOS, inducible isoform of nitric oxide synthases; MTrS, myofascial trigger spot; SP, substance P; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; s1D, sham one-dosage dry needling; s5D, sham five-dosage dry needling.

was blinded to the group assignment regarding the needling dosage. Dry needling stimulation was performed with a disposable 30G acupuncture needle (300 μm in diameter, 1.5 in length, Yu-Kuang Industrial Co., Ltd., Taiwan). The technique used was similar to the other methods used in our previous studies [25, 32]. In needling the MTrS of the biceps femoris, the needle was first inserted perpendicularly through the skin at the center of the marked spot. The needle was then advanced slowly and gently into the muscle until the needle tip touched the bone surface to estimate the thickness of the muscle. Needle rotation was simultaneously performed to facilitate a fast "in-and-out" needle movement, eliciting as many LTRs as possible. Sham needling was performed by inserting the needle into the subcutaneous layer of the marked MTrS region at a depth of approximately 1 mm to 2 mm from the skin surface. The needle remained inserted without any further movement.

2.6. Serum and Tissue Preparations. Blood (1 mL) was drawn from the marginal ear vein of the rabbit under light anesthesia (4% isoflurane) before and after treatments for five rabbits from each group. Blood samples were collected on chilled glass tubes and then left in an ice-filled bucket for 3 h to 4 h at −80°C until the day of the experiment. After the treatment, the rest of the animals were immediately sacrificed (i.e., without having blood samples drawn from them) with strong anesthesia by injecting saturated KCl (300 g/mL, intraperitoneal injection) to harvest the biceps femoris muscle containing the taut band and its ipsilateral corresponding segment of L2–L5 DRG for the immunoassays. The muscle specimens were cut through the midline and were then divided into two portions to obtain identical specimens for immunohistochemical staining and immunoassays. For immunohistochemical staining, the muscle specimens were fixed in 10% neutral formalin and then embedded in paraffin for 12 h at room temperature. For the immunoassays, the specimens were homogenized in T-PER Tissue Protein Extraction Reagent (Pierce Chemical Co., IL, USA) and the complete cocktail of protease inhibitors (Sigma, NY, USA). After centrifugation, the supernate was extracted and stored at −80°C. The specimen biceps femoris muscles with nontaut bands were also harvested from some rabbits. The specimens were then submitted for hematoxylin and eosin (H&E) staining to identify and compare the morphology of taut and nontaut bands within a muscle.

2.7. Enzyme-Linked Immunosorbent Assay (ELISA). The levels of serum β-endorphin and TNF-α were determined by ELISA (β-endorphin: Catalog no. E0806Rb, EIAab Science Co., Ltd., Wuhan, China; TNF-α: DuoSet ELISA Development kit R&D Systems, Minneapolis, MN, USA). Specimen extracts were incubated in 96-well plates coated with an antibody specific to β-endorphin or TNF-α. Biotin-conjugated β-endorphin or TNF-α and horseradish peroxidase-conjugated streptavidin (HRP) were added and incubated according to manufacturer's instructions. After washing, a tetramethylbenzidine substrate solution was added. The enzyme reaction was terminated by adding a stop solution containing sulfuric acid. The concentration of β-endorphin in serum and TNF-α in the biceps femoris was assessed with a reader (Thermo Scientific Multiskan EX, Finland) using a 450 nm filter and normalized with an abundance of the standard solution. Data were then analyzed using Ascent Software (Thermo Scientific Ascent Software, Finland) and a four-parameter logistic curve fit.

2.8. Western Blot Analysis. Protein determination was performed using modified Lowry protein assays. Equal amounts of protein were loaded and separated in 10% Tris-Tricine SDS-PAGE gels. The resolved proteins were then transferred onto polyvinylidene fluoride membranes (Millipore, Bedford, MA, USA). The membranes were blocked in 5% nonfat milk for 1 h at room temperature and then incubated overnight with primary antibodies against β-endorphin (Cat. # ab8907, Abcam, Cambridge, UK), substance P (Cat. # orb11399, Biorbyt, Cambridge, UK), HIF-1α (NB100-105, Novus Biologicals, CA, USA), VEGF (Cat. # 205907, Abbiotec, CA, USA), iNOS (Cat. # AB5382, Millipore, CA. USA), COX-2 (Cat. # 250609, Abbiotec, CA, USA), and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (ab8245, Abcam Inc, MA, USA) at a dilution of 1 : 2500 in a blocking solution. The blots were then incubated with the HRP-conjugated goat anti-mouse and anti-rabbit anti-Immunoglobulin G (IgG) secondary antibody (1 : 20000, Jackson ImmunoResearch Laboratories, Inc., West Grove, PA, USA) for 1 h at room temperature. The signals were finally visualized using an enhanced chemiluminescence detection system (Fujifilm LAS-3000 Imager, Tokyo, Japan), and the blots were exposed to X-ray. All Western blot analyses were performed at least three times, and consistent results were obtained. The immunoreactive bands were analyzed using computer-based densitometry Gel-Pro Analyzer Version 6.0 (Media Cybernetics, Inc. USA). The gray levels obtained from the densitometric analysis of the immunoreactive bands were normalized with GAPDH (14C10, Cell Signaling Technology, Danvers, MA, USA).

2.9. Immunohistochemical Staining and Quantitative Analysis. The specimens were subjected to xylene diaphanisation, dehydrated using graded ethanol, embedded in paraffin, and then sliced using a microtome into 4 μm thick cross sections. Each muscle specimen produced approximately 20 sections. For immunohistochemical staining, the slides were first incubated overnight at 4°C with a monoclonal mouse anti-TNF-α antibody (1 : 200, ab1793, Abcam, MA, USA). The muscle sections were then incubated with biotinylated goat anti-mouse IgG secondary antibody (Jackson ImmunoResearch Laboratories, Inc., West Grove, PA, USA) for 1 h at room temperature. After washing the sections, they were incubated with a streptavidin-HRP conjugate (Jackson ImmunoResearch Laboratories, Inc., West Grove, PA, USA). The sections were visualized as brown precipitates by adding 0.2 mg/mL 3,3′-diaminobenzidine (DAB) (Pierce, Rockford, IL, USA) as a substrate. The sections were then counterstained with hematoxylin. The immunohistochemically stained sections were examined under a light microscope (BX43, Olympus America Inc., NY, USA).

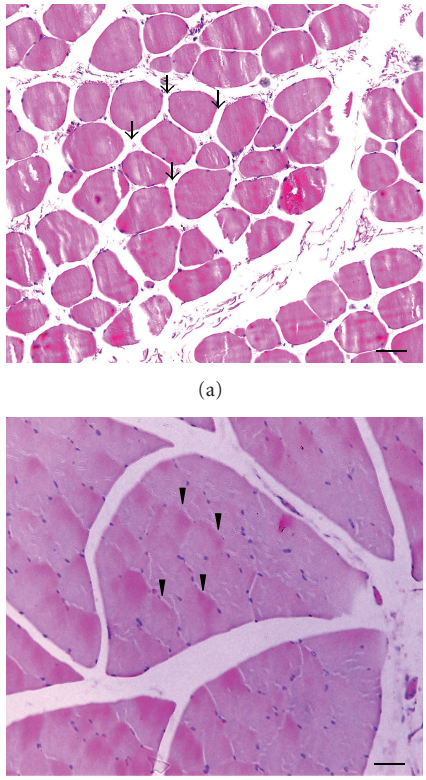
The slides were examined and photographed at five randomly selected fields at 200x magnification under a light microscope (BX43, Olympus America Inc., NY, USA) and with a 1360 pixels $\times$ 1024 pixels cooled digital color camera (DP70, Olympus America Inc., NY, USA). The images were saved and adjusted to equalize contrast and brightness by using Adobe Photoshop (CS3, San Jose, CA); no other modifications were made. The digital images were analyzed by computer-based morphometry using ImageScope software package with the Color Deconvolution v9 tool (v9.1.19.1571, Aperio, Vista, CA, USA). Based on the automatically calculated parameters, the number of DAB-stained strong-positive staining cells in each section was measured for TNF-α-like immunoreactivity (TNF-LI).

2.10. Statistical Analysis. Experiments were repeated at least five times for each sample. The relative intensity of the Western blot band for each protein was normalized to the GAPDH protein level, expressed as a percentage of its sham value. The data are expressed as mean $\pm$ standard deviation. The differences in the contents of β-endorphin, substance P, TNF-α, COX-2, HIF-1α, iNOS, and VEGF among the four groups were determined by ANOVA. Scheffe's method was used to perform post hoc comparisons among groups. A P value of <0.05 was considered statistically significant. All data were analyzed using SPSS version 10.0 for Windows (SPSS Inc., IL, USA).

3. Results

3.1. Histopathological Evaluation of the Biceps Femoris with a Taut Band and a Nontaut Band. In the histomorphometric analysis by H&E staining, the nontaut band portion of the biceps femoris muscle showed a skeletal muscles with normal morphology, characterized by polygonal fibers with multiple nuclei arranged on the periphery of the cell and a clear space of endomysium enveloping each muscle fiber (Figure 2(a)). However, the endomysium enveloping each muscle fiber in the taut band of the biceps femoris was narrow and cramped, suggesting an enlargement of muscle fibers due to shortening and tightness of the contractile unit or focal muscle edema (Figure 2(b)).

3.2. Effects of Dry Needling on the Protein Levels of β-Endorphin in the Biceps Femoris and Serum. The protein levels of β-endorphin in the biceps femoris for the 1D, s1D, 5D, and s5D groups are presented in Figure 3(a). Immediately after



(a)

(b)

Figure 2: Morphological findings of representative skeletal muscles with nontaut and taut bands. (a) Biceps femoris with a nontaut band; (b) Biceps femoris with a taut band (H&E staining, scale bar = 5 μm).

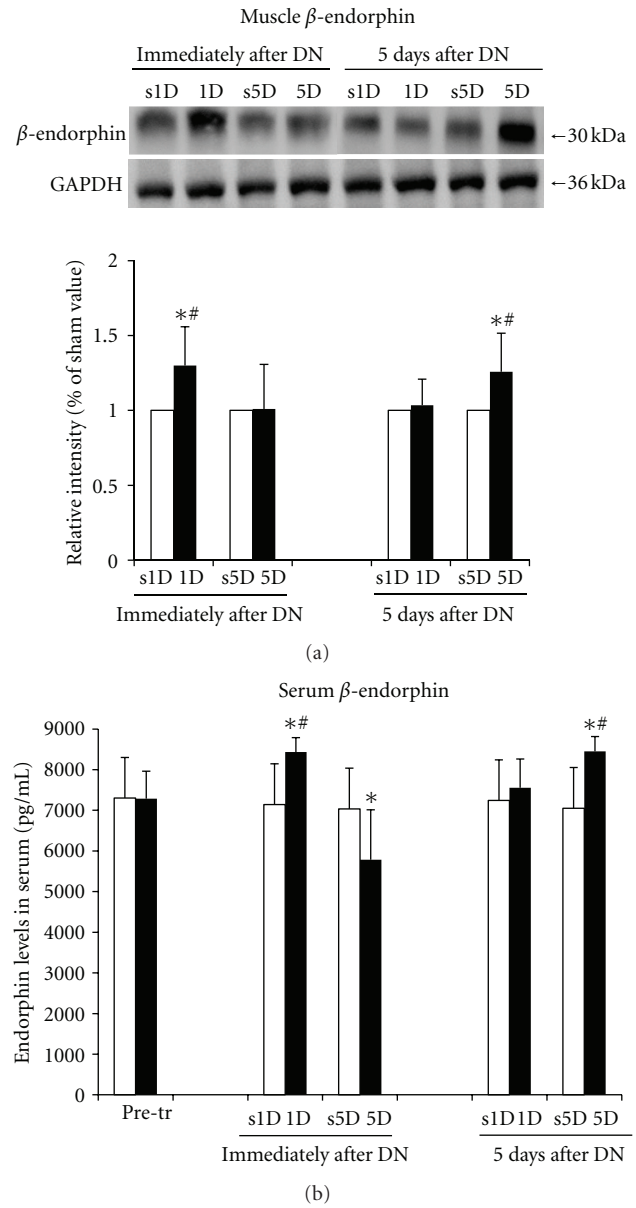


Figure 3: Effects of one- and five-dosage (1D, 5D) dry needling on β-endorphin expression in the needling-treated muscle and serum. The levels of β-endorphin in the muscle and serum obtained by (a) Western blot analysis and (b) ELISA. A representative Western blot image of a muscle tissue is shown (upper panel of (a)). The quantification of the protein levels is expressed as mean ± SD. *Indicates a significant difference ($P < 0.05$) between the sham groups (s1D and s5D). #Represents the significant difference ($P < 0.05$) between the 1D and 5D groups. DN: dry needling.

treatment, the protein levels of β-endorphin in the needling-treated biceps femoris significantly increased in the 1D group compared with the s1D group ($P < 0.05$). No significant difference in the protein levels of β-endorphin was indicated between the 5D and s5D groups ($P > 0.05$). However, 5 d after dry needling, the β-endorphin levels in the biceps femoris significantly increased in the 5D group ($P < 0.05$) and remained the same in the 1D group ($P > 0.05$).

The protein levels of serum β-endorphin determined by ELISA for the 1D, s1D, 5D, and s5D groups are shown in Figure 3(b). No significant difference in the serum β-endorphin levels between the s1D and s5D groups was indicated before, immediately after, and 5d after the treatment (all $P > 0.05$). Serum β-endorphin significantly increased immediately after the 1D treatment ($P < 0.05$) but significantly decreased immediately after the 5D treatment ($P < 0.05$). Five days after dry needling, serum β-endorphin significantly increased in the 5D group ($P < 0.05$) but not significantly changed in the 1D group ($P > 0.05$). Significant differences between the 1D and 5D groups were observed immediately and 5 d after treatment (all $P < 0.05$).

Significant differences in the β-endorphin levels in the biceps femoris and the DRG were determined between the 1D and 5D groups immediately and 5 d after treatment (all $P < 0.05$). The biceps femoris and serum in the 1D group showed higher levels of β-endorphin compared with the 5D group immediately after treatment (all $P < 0.05$). However, these levels were lower in the 5D group than in the 1D group 5 d after treatment (all $P < 0.05$).

3.3. Effects of Dry Needling on the Protein Levels of Substance P in the Biceps Femoris and the DRG. The protein levels of substance P in the biceps femoris of the 1D, s1D, 5D, and s5D

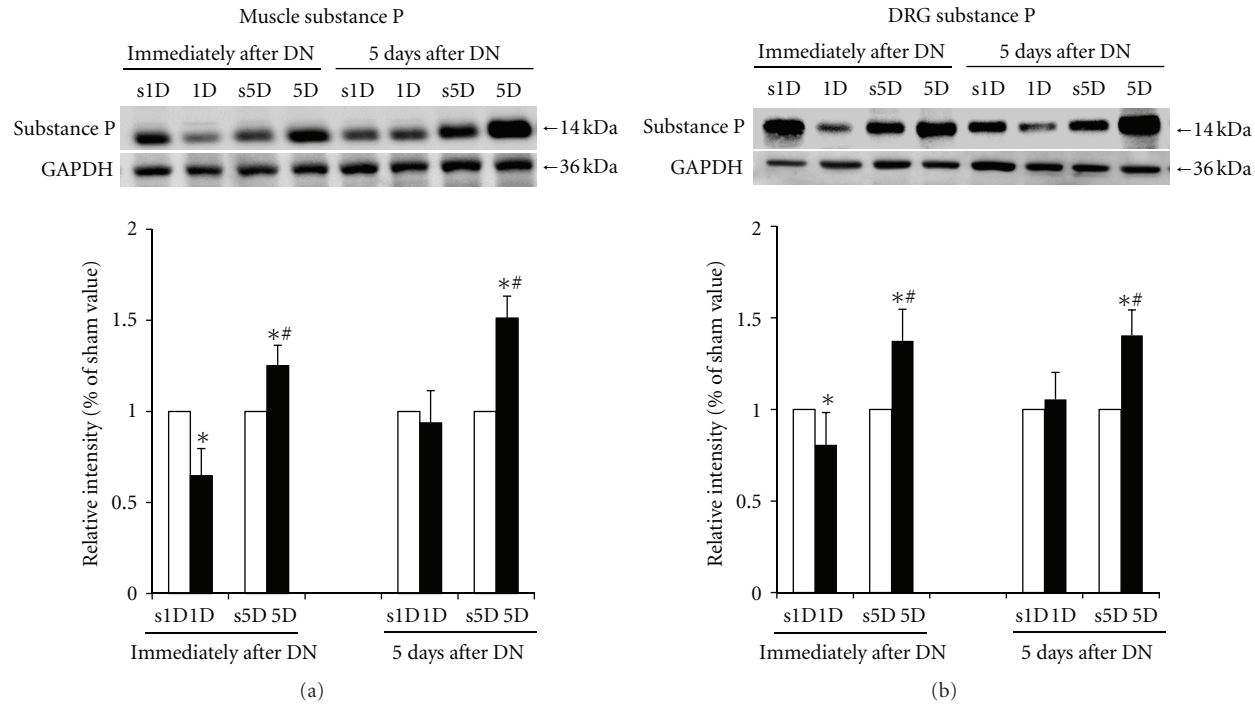


Figure 4: Effects of one- and five-dosage dry needling (1D, 5D) on substance P expression in a (a) needling-treated muscle and (b) DRG. Representative Western blot images are presented on the upper panels of (a) and (b). The quantification of the protein levels is expressed as mean ± SD. *Indicates the significant difference ($P < 0.05$) between the sham groups (s1D and s5D). #Represents the significant difference ($P < 0.05$) between the 1D and 5D groups. DN: dry needling.

groups are shown in Figure 4(a). The protein levels of substance P in the needling-treated biceps femoris significantly decreased in the 1D group compared with the s1D group immediately after treatment ($P < 0.05$). However, immediately after 5D dry needling, the substance P protein in the biceps femoris significantly increased compared with the s5D group ($P > 0.05$). Five days after dry needling, no significant differences in the protein levels of substance P were observed between the 1D and s1D groups ($P > 0.05$). However, a prolonged increase in substance P in the biceps femoris was observed in the 5D group compared with those in the s5D group ($P < 0.05$).

The protein levels of substance P in L2–L5 DRG with the corresponding innervations of the biceps femoris for the 1D, s1D, 5D, and s5D groups are shown in Figure 4(b). These results were similar to the protein levels of substance P in the biceps femoris.

Significant differences in substance P of the biceps femoris and DRG were observed between the 1D and 5D groups at the time points immediately and 5 d after treatment (all $P < 0.05$). Higher levels of substance P in the biceps femoris and the DRG were found in the 5D group compared with those in the 1D group at the time points immediately and 5 d after treatment (all $P < 0.05$).

3.4. Effect of Dry Needling on the Protein Levels of iNOS, HIF-1α, COX-2, and VEGF in the Biceps Femoris. The protein levels of iNOS, HIF-1α, COX-2, and VEGF in the biceps femoris for the 1D, s1D, 5D, and s5D groups are shown in Figure 5. No significant differences in the protein levels of iNOS, HIF-1α, COX-2, and VEGF were observed between the 1D and s1D groups at the time points immediately and 5 d after dry needling ($P > 0.05$). However, after the 5D dry needling, the levels of iNOS, HIF-1α, COX-2, and VEGF proteins were significantly higher than those in the s5D group (all $P < 0.05$). The increase was prolonged and observed 5 d after the 5D dry needling (all $P < 0.05$).

Significant differences in the protein levels of iNOS, HIF-1α, COX-2, and VEGF between the 1D and 5D groups were indicated at the time points immediately and 5 d after treatment (all $P < 0.05$). Higher levels of iNOS, HIF-1α, COX-2, and VEGF in the biceps femoris were observed in the 5D group compared with those in the 1D group at the time points immediately and 5 d after treatment (all $P < 0.05$).

3.5. Immunoassays for TNF-α in the Biceps Femoris and Serum after Dry Needling. Immunohistochemical analysis of the 1D and 5D groups showed that the biceps femoris sections of the rabbits exhibited marked inflammatory cell infiltration and more TNF-LI cells along the needling path compared with the s1D and s5D groups immediately after dry needling (all $P < 0.05$; Figures 6(a), 6(b), 6(c), 6(d), and 6(i)). Five days after dry needling, both 1D and 5D groups continued showing marked inflammation along the needling path compared with the s1D and s5D groups (all $P < 0.05$; Figures 6(e), 6(f), 6(g), and 6(h)). The needling-treated muscle in the 1D group almost healed with a slight inflammatory cell accumulation. In the 5D group, the muscle had

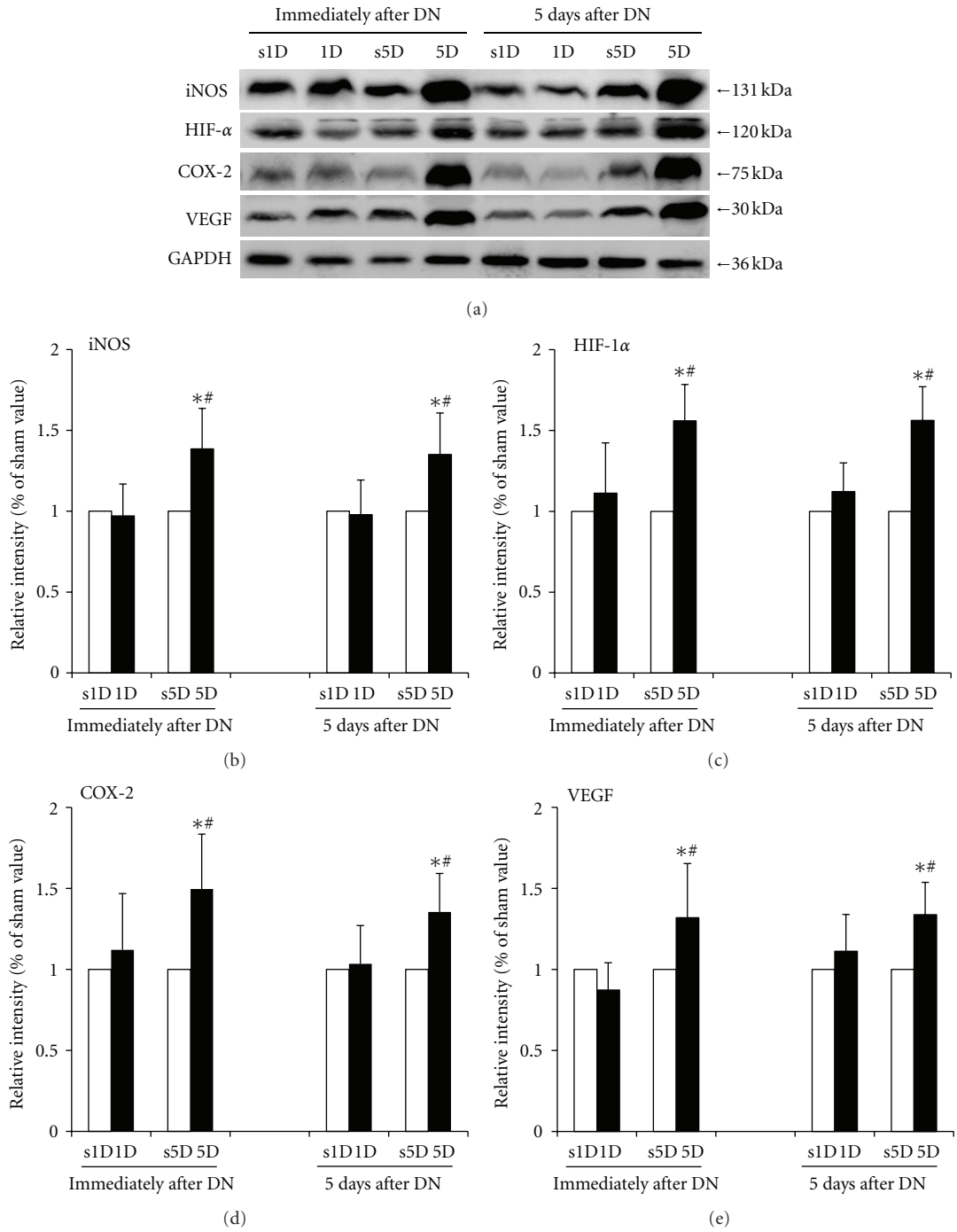


Figure 5: Effects of one- and five-dosage dry needling (1D, 5D) on iNOS, HIF-1α, COX-2, and VEGF expressions in a needling-treated muscle. (a) Representative Western blot images. The quantification of the protein levels for (b) iNOS, (c) HIF-1α, (d) COX-2, and (e) VEGF. Values are expressed as mean ± SD. *Indicates the significant difference ($P < 0.05$) between the sham groups (s1D and s5D). #Represents the significant difference ($P < 0.05$) between the 1D and 5D groups. DN: dry needling.

not fully healed 5 d after dry needling, with some inflammatory cells and TNF-LI cells clustered in the needling area. Scarring in the needling area was evident. In the 5D group, the inflammatory and TNF-LI cells significantly increased and were overexpressed compared with those in the 1D group immediately and 5 d after dry needling (all $P < 0.05$, Figure 6(i)). In the s1D and s5D control groups, the muscle fibers exhibited regularly arranged fascicles without degeneration, hemorrhage, necrosis, inflammatory cell infiltration, or TNF-LI cell accumulation. The protein levels of TNF-α

in serum assessed by ELISA also increased significantly in the 1D and 5D groups compared with those in the s1D and s5D groups (all $P < 0.05$, Figure 6(j)). These results obtained by ELISA were similar to those obtained by immunohistochemistry.

Significant differences were indicated in the TNF-α levels of the biceps femoris and serum between the 1D and 5D groups immediately and 5 d after treatment (all $P < 0.05$). Higher levels of TNF-α in the biceps femoris and serum were observed in the 5D group compared with those in the 1D group immediately and 5 d after treatment (all $P < 0.05$).

4. Discussion

Table 1 summarizes the main results of the study. This study is the first to report on assessing biochemical alterations after dry needling MTrSs in a well-established animal model. Our findings suggested differences in the dry needling-modulated biochemicals associated with pain, inflammation, and hypoxia between the 1D and 5D treatments. These variations are dosagedependent and based on the levels of substance P and β-endorphin, as well as those of TNF-α, iNOS, HIF-1α, COX-2, and VEGF.

4.1. Short-Term Dry Needling Modulates the Biochemicals Associated with Pain and Inflammation. In this study, substance P, β-endorphin, and TNF-α were responsive to a short-term (1D) dry needling treatment. The effects on these biochemicals associated with pain and inflammation showed the following: (1) immediately after the 1D treatment, an increase in the TNF-α levels in the biceps femoris and the β-endorphin levels in the biceps femoris and serum was accompanied by a reduction in the substance P levels of the biceps femoris and DRG; and (2) 5 d after the 1D treatment, these variations in the substance P and β-endorphin levels were not observed, but TNF-α continued to accumulate along the needling path in the biceps femoris through which the needle was manipulated in and out.

Peripheral opioid analgesia has received considerable attention as an endogenous pathway of inhibiting pain. Studies showed that increasing the β-endorphin level in the inflamed tissues can cause analgesia [33, 34]. Acupuncture was demonstrated to enhance the secretion of endogenous opioid and β-endorphin in blood plasma to produce a strong analgesic effect and control pain in peripheral tissues [35]. Opioids are anti-inflammatory because they inhibit the release of neuroinflammatory mediators, including substance P [10]. An electroacupuncture treatment can reduce the mechanical allodynia in a mouse model of cancer pain because of a consequent decrease in substance P levels in the spinal dorsal horn and an increase in β-endorphin levels in the blood and the brain [36]. Shah et al. found elevated levels of substance P in subjects with an active MTrP in the upper trapezius muscle during needle insertion. The elicitation of an LTR resulted in a significant decrease in substance P concentration [9, 11]. Our result showing the decrease in dry needling-evoked substance P was consistent with that in the study by Shah et al. [9, 11]. The data obtained from this study suggested that the 1D treatment produces a short-term analgesic effect by modulating the substance P and β-endorphin levels in peripheral sites; however, no lasting effect was observed 5 d after dry needling.

Table 1: Summary of the biochemical effects in the bicep femoris, DRG, and serum affected by one- and five-dosage dry needling in the biceps femoris with MTrSs.

Biochemicals	Immediately after DN		5 days after DN	
	1D	5D	1D	5D
Biceps femoris				
β-endorphin	↑	—	—	↑
Substance P	↓	↑	—	↑
TNF-α	↑	↑↑	↑	↑↑
iNOS	—	↑	—	↑
HIF-1α	—	↑	—	↑
COX-2	—	↑	—	↑
VEGF	—	↑	—	↑
DRG				
Substance P	↓	↑	—	↑
Serum				
β-endorphin	↑	↓	—	↑
TNF-α	↑	↑↑	↑	↑↑

↑ indicates the significant increase in dry needling-treated groups compared with their sham groups. ↓ indicates reduction of Substance P in 1D group immediately after DN. ↑↑ indicates the significant increase in the 5D group compared with the 1D group. — indicates no significant difference between the dry needling-treated groups and the sham groups. Abbreviations: 1D: one-dosage dry needling; 5D: five-dosage dry needling; COX-2: cyclooxygenase-2; DN: dry needling; DRG: dorsal root ganglion; HIF-1α: hypoxia-inducible factor-1α; iNOS: inducible isoform of nitric oxide synthases; TNF-α: tumor necrosis factor-α; VEGF: vascular endothelial growth factor.

A systematic review showed marked improvements in patients with MPS in which MTrPs were directly needled, suggesting that dry needling therapy has a specific efficacy in the treatment of pain arising from MTrPs [18]. However, some clinical trials demonstrated that dry needling achieves only short-term alleviation of pain and improvement of function [37, 38]. Our biochemical findings described above suggest that one mechanism by which short-term dry needling produces brief analgesia in MPS may be the enhancement of peripheral β-endorphin in the serum and the biceps femoris.

4.2. Long-Term Dry Needling Modulates the Biochemicals Associated with Pain, Inflammation, and Hypoxia. In addition to alterations of substance P, β-endorphin, and TNF-α caused by the 1D treatment, COX-2, HIF-1α, iNOS, and VEGF were more responsive to long-term (5D) dry needling treatment. For these biochemicals associated with pain, inflammation, and hypoxia, the following was observed: (1) immediately after the 5D treatment, TNF-α, iNOS, HIF-1α, COX-2, VEGF, and substance P levels were enhanced in the needling-treated muscle, accompanied by an increase in substance P in the DRG and a reduction in serum β-endorphin level; and (2) 5 d after the 5D treatment, these higher levels of TNF-α, iNOS, HIF-1α, COX-2, VEGF, and substance

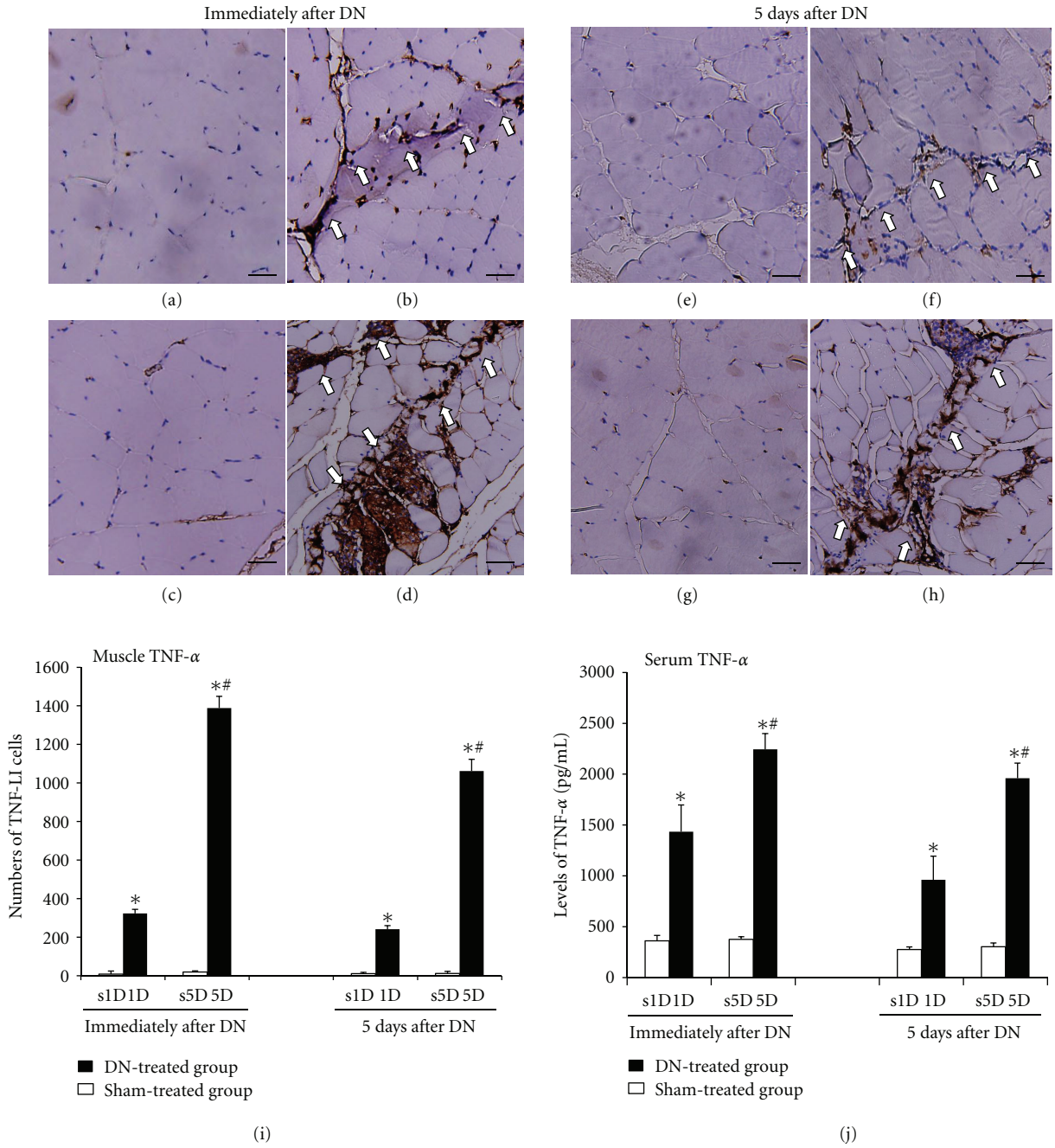


Figure 6: The variation in TNF-α after one- and five-dosage dry needling (1D, 5D) in the biceps femoris with a taut band in the experimental (1D, 5D) and sham groups (s1D, s5D). Representative photomicrographs indicate the immunohistochemical labeling for TNF-α in the muscle immediately after dry needling: (a) s1D, (b) 1D, (c) s5D, and (d) 5D, as well as 5 d after dry needling: (e) s1D, (f) 1D, (g) s5D, and (h) 5D. Histograms indicate the quantitative analysis of (i) TNF-LI cells and (j) protein levels of TNF-α by applying ELISA in the serum. *Indicates the significant difference ($P < 0.05$) between the sham groups (s1D and s5D). #Represents the significant difference ($P < 0.05$) between the 1D and 5D groups. DN: dry needling. (scale bar = 5 μm).

P were maintained, whereas the β-endorphin levels in the biceps femoris and serum increased. The 5D treatment of the biceps femoris with a taut band and MTrSs seemed to have a higher dosage than the 1D treatment; the 5D treatment may not have provided a suitable stimulus to activate β-endorphin and reduce the substance P level. TNF-α and COX-2 were implied to be involved in this possible damage of intensive dry needling. This result was supported by a study demonstrating that exercise-induced muscle damage was associated with an increase in COX-2 and TNF-α levels [39].

In this study, TNF-α overexpression was found in some traces of the needle penetrating into the biceps femoris. Although TNF-α levels in the biceps femoris and serum were enhanced by dry needling either in the 1D or the 5D

treatment, abundant TNF-α accumulation and inflammatory cells were observed immediately and 5 d after the 5D treatment. The 5D treatment-activated COX-2 level was also higher than the 1D treatment in the biceps femoris. The increase in COX-2 expression was shown to be associated with the release of substance P, evoked by noxious stimuli from cultured DRG neurons [40]. A more likely possibility is that 5D is an overloaded invasive manipulation to cause excess damage in the skeletal muscle fibers, stimulate excessive noxious inputs, and increase the release of substance P. The result of this study indicates that pain level was raised after long-term dry needling. Our results also showed that β-endorphin increases in 5D group 5 days after dry needling, but not immediately after dry needling. This result could be supported by a study demonstrating that the β-endorphin messenger RNA expression was more predominate in the later phases of inflammation (peaking on day 14), leading to attenuated pain responses [41]. Whereas 5D increased the β-endorphin levels 5 d after ceasing treatment, the substance P levels in both the biceps femoris and the DRG did not decrease. This result could be supported by a human study demonstrating that an increased level of β-endorphin is insufficient to inhibit pain in the temporomandibular joint [42].

More studies showed that HIF-1α upregulation can be induced not only by hypoxic stress but also mechanical stress [43]. Induction of HIF target genes, including VEGF and iNOS, can promote angiogenesis, vasodilation, and altered glucose metabolism in hypoxic tissues [44, 45]. Studies using enhanced HIF-1α expression suggest that HIF-1α upregulation is a beneficial therapeutic modality for hypoxia/ischemia [45, 46]. The region containing numerous MTrPs can become focally ischemic because of limited oxygen supply by compression of the muscle contracture [2, 3]. Human studies also suggest that local, temporary hypoxia and blood flow reduction within muscle fibers in patients with trapezius myalgia, as well as the degree of hypoxia and impaired circulation, are correlated of pain intensity [47–49]. Our results also show that the 5D treatment can enhance HIF-1α, iNOS, and VEGF production in the needling-treated muscle. Thus, the increases in HIF-1α protein levels can upregulate VEGF protein expression, potentially increasing capillarity in the skeletal muscle. Therefore, the expression of HIF-1α, iNOS, and VEGF proteins can be key to improving circulation in muscles containing MTrSs after intensive dry needling. However, the long-term effects (>5 d) on the circulation after the 5D treatment remain unclear and need a long-term, follow-up study.

In addition, a skeletal muscle is a dynamic tissue with an extraordinary capacity for repair after an injury [50]. TNF-α, iNOS, and VEGF are essential molecules involved in cellular events to activate the formation of new blood vessels and repair injured muscles in the process [50–52]. In this study, the 5D treatment enhanced the expression of these proteins, and thus, a 5D-induced muscle injury that can promote the rearrangement and repair of skeletal muscles with a taut band is of particular interest. Prevention of muscle fibrosis is the main objective of improving muscle healing following an injury from 5D. A further follow-up study must be conducted to investigate whether intensive trigger point dry needling of 5D affects the rearrangement of skeletal muscles with a taut band.

4.3. Limitation of the Study. The primary disadvantage of this study is the lack of pain behavioral assessments to confirm the correlation between the alterations of biochemicals and the intensity of muscle pain after the 5D repetitive manipulation of dry needling in rabbits. Using our multiple quick insertion technique, we observed that long-term dry needling was much less effective compared with short-term dry needling in alleviating pain. We speculate that the sharp tip of the acupuncture needles causes additional muscle damage after the 5D treatment. A human study demonstrated that visual analog scales were not significantly decreased after six sessions of dry needling compared with the placebo group. The authors conclude that multiple insertions of dry needling with a blunt needle caused one type of local muscle injury, causing pain in the treatment of MPS [53]. In addition, dry needling using an acupuncture needle can cause even more severe damage compared with blunt needles [53]. Therefore, the 5D treatment using an acupuncture needle can increase the biochemicals associated with inflammation and pain because of excessive muscle damage, thus increasing the intensity of pain.

5. Conclusion

The hypothesis that dry needling at MTrSs can modulate biochemicals associated with pain, inflammation, and hypoxia depending on the dry needling dosage is supported by our data. The findings of this study can clarify the biochemical mechanisms induced by dry needling. This study can elucidate the analgesic action of dry needling in treating soft tissue systems and lead to the development of new therapeutic strategies to treat MPS.

Disclosure

No commercial party having a direct financial interest in the results of the research supporting this paper has or will confer a benefit upon the authors or upon any organization with which the authors are associated.

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Research Article

Percutaneous Soft Tissue Release for Treating Chronic Recurrent Myofascial Pain Associated with Lateral Epicondylitis: 6 Case Studies

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Objective. The purpose of this pilot study is to investigate the effectiveness of the percutaneous soft tissue release for the treatment of recurrent myofascial pain in the forearm due to recurrent lateral epicondylitis. *Methods*. Six patients with chronic recurrent pain in the forearm with myofascial trigger points (MTrPs) due to chronic lateral epicondylitis were treated with percutaneous soft tissue release of Lin's technique. Pain intensity (measured with a numerical pain rating scale), pressure pain threshold (measured with a pressure algometer), and grasping strength (measured with a hand dynamometer) were assessed before, immediately after, and 3 months and 12 months after the treatment. *Results*. For every individual case, the pain intensity was significantly reduced ($P < 0.01$) and the pressure pain threshold and the grasping strength were significantly increased ($P < 0.01$) immediately after the treatment. This significant effectiveness lasts for at least one year. *Conclusions*. It is suggested that percutaneous soft tissue release can be used for treating chronic recurrent lateral epicondylitis to avoid recurrence, if other treatment, such as oral anti-inflammatory medicine, physical therapy, or local steroid injection, cannot control the recurrent pain.

1. Introduction

Myofascial pain is a frequent complaint in clinical practice [1–4]. One or more myofascial trigger points (MTrPs) can usually be identified in the muscles responsible for myofascial pain [4]. An MTrP is the most irritable spot in a taut band of skeletal muscle [1, 4], probably due to accumulation of sensitized nociceptors [2, 3]. Almost every normal adult has latent MTrPs, those, which are tender but not painful spontaneously. It becomes active via central sensitization as a consequence of neural or musculoskeletal lesion near or remote to this MTrP [2, 3, 5–7]. An active MTrP is painful spontaneously or in response to movement involving that muscle [4]. An active MTrP can be inactivated after appropriate myofascial pain therapy [4], but recurred frequently if the underlying etiological lesion is not completely removed [2, 3, 6, 8–10]. In clinical practice, an active MTrP can be inactivated immediately after an MTrP injection, but the pain frequently recurs 2-3 weeks after the injection [8, 9]. It appears that the underlying lesion that causes the activation of MTrP is not eliminated [2, 3, 6, 9, 10]. One common example is the pain in the forearm due to MTrPs in the forearm muscles in response to chronic lateral epicondylitis of elbow.

Lateral epicondylitis (the so-called tennis elbow) is a common elbow pain in clinical practice. It is usually diagnosed in patients with pain over the radial aspect of the elbow, worsened by repetitive or excessive movements of wrist with the elbow in extension, and aggravated by resistive contraction of wrist extensors [11–13]. In addition to

Table 1: Demographic data of patients.

Case	A	B	C	D	E	F	Mean
Ages (years)	35	48	42	38	53	33	41.5 ± 7.8
Sex	M	F	F	M	M	F	
Side (right/left)	R	R	L	L	R	R	
Duration of pain (years)	3.8	5.2	3.3	2.5	3.1	2.7	3.4 ± 1.0
Trauma history	Sports	None	Traffic accident	None	Sports	None	
Occupation	School teacher	Housewife	Secretary	Constructor	Manager	Housewife	
Previous therapies							
Oral NSAID (months)	12	40	24	30	30	24	26.7 ± 9.3
Physical therapy (months)	18	30	20	12	14	15	18.2 ± 6.5
Local steroid (times)	3	5	3	3	4	2	3.3 ± 1.0
Duration of effectiveness (months)	2-3	3-4	2–4	3–5	3-4	1–3	

the localized pain in the elbow, it can also cause myofascial pain in the wrist and hand extensors [4].

The initial management of lateral epicondylitis is conservative [4, 12, 14], with the use of rest, activity modification, nonsteroidal anti-inflammatory drugs, forearm bracing [15], physiotherapy, and local steroid injections [16]. These treatments can provide a transient remission for few months in up to 90% of patients, and 3–8% of patients, who are refractory to conservative treatment, may be surgical candidates [14].

Operative management for lateral epicondylitis remains controversial [12]. Since 1922, 14 main surgical treatments modalities with some 300 modifications, have been described [12, 17]. However, it is still unknown whether a given surgical procedure is to be preferred, why each of the different modifications of surgery reports such high success rates, and why some patients fail to respond to surgery [12]. The answer probably lay in the methodology applied in each of these studies [12].

Percutaneous release of common extensor tendons at the lateral epicondyle has been used for treating recurrent lateral epicondylitis [18–23]. A sharp surgical knife or an 18G needle (with sharp cut edge) was used for this procedure.

To avoid excessive tissue damage and bleeding, the first author has developed a new technique by using a cosmetic needle for the release of adhesive soft tissues between the tendon sheath and the periosteum. We have found that this technique can provide successful relief of pain for a significantly long period. This technique is much less invasive comparing to the surgical technique or percutaneous needle release reported previously as mentioned above.

This pilot study is designed to assess the quantitative effectiveness of percutaneous soft tissue release for treating myofascial pain due to lateral epicondylitis.

2. Materials and Methods

2.1. Patients. Six selected patients with chronic recurrent pain in one elbow and ipsilateral posterior forearm muscles were included in this study. We selected those patients based on the following conditions (standard for this procedure set up by the authors): (1) chronic pain in the lateral epicondyle of one elbow (diagnosed as lateral epicondylitis) and ipsilateral posterior forearm muscles (diagnosed as myofascial pain) for longer than 2 years, (2) treated with physical therapy and oral nonsteroid anti-inflammatory drugs for more than one year with poor results, and (3) treated with local steroid injection with temporary pain relief but recurred within 6 months. We did not include patients with the following conditions: (1) the patient with cognitive deficit, (2) the patient with history of neurological or orthopedic disorder of the involved limb other than pain due to lateral epicondylitis, (3) the patient with any serious medical problem, and (4) the pregnant patient.

The diagnosis of lateral epicondylitis included the following criteria: pain of lateral epicondyle over the radial aspect of the elbow, worsened by repetitive or excessive movements of wrist with the elbow in extension, a tender spot over the lateral epicondyle, and aggravated by resistive contraction of wrist extensors [11–13].

The diagnosis of myofascial pain was based on the exist of MTrPs in one or more muscles in the involved posterior forearm (muscles originate from the common tendon originated from the lateral epicondyle). The criteria for the diagnosis of MTrP included an exquisite tender spot in a palpable taut band of muscle fibers located at the sites indicated in Travell's trigger point manual [1], referred pain or referred tenderness following the patterns described by Travell and Simons [1], and local twitch response in response to the snapping palpation of this spot [1, 4].

The Institutional Review Board of the university approved the study and all subjects signed the informed consents for this paper and the assessments with noninvasive routine procedures in the pain clinic.

The characteristics of these 6 patients are listed in Table 1.

2.2. Percutaneous Soft Tissue Release. Lin [24] has developed a new technique to release the adhesive tissues due to soft tissue lesion by using a blunt cannula (Figure 1). This blunt cannula is originally developed for cosmetic procedure to inject hyaluronic acid into the face or any other tissue. Initially, this procedure had been performed with dry needling. However, the patient developed sore pain

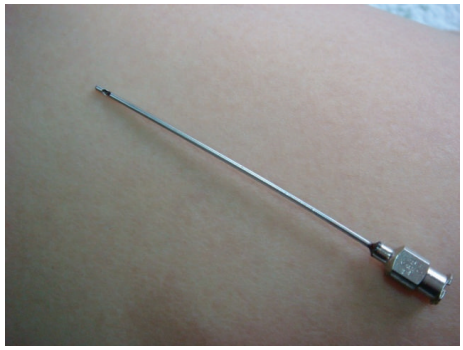

Figure 1: Cosmetic needle used for percutaneous soft tissue release.

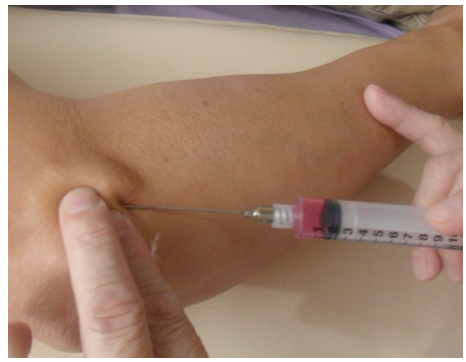

Figure 2: Needle holding for percutaneous soft tissue release.

for few days after the procedure. Therefore, injection of 1% lidocaine, cortical steroid, and hyaluronic acid was given via a 10 cc syringe connected to the blunt cannula. The addition of local anesthetic was for the immediate relief of pain and also to provide information about the effectiveness of this procedure immediately after treatment. Corticosteroid was used as a strong anti-inflammatory agent. Hyaluronic acid was used for lubrication to avoid readhesion.

Initially, the skin around the lateral epicondyle (the origin sites of the common tendons of hand/finger extensors) was cleaned up with povidone-iodine (Betadine). Then, under local anesthesia, the skin was penetrated with an 18 G injection needle to make a hole for the penetration of this blunt cannula. By holding the 10 cc syringe (containing solution as mentioned above) with the dominant hand (Figure 2), the cannula was inserted into the hole to reach the subcutaneous tissue layer, and then moved toward the painful region of the lateral epicondyle slowly. In addition to the forward needle movement, side movement was also performed to release the soft tissues above the common extensor tendons around this track. During needle movement, a drop of solution in the syringe was injected whenever patient complained any pain or discomfort from the needle movement. When the resistance of needle movement was reduced, the needle was pulled back to the subcutaneous layer, and then turned to a different direction for a new track of penetration. Similar to the multiple insertion technique of MTrP injection [9, 25], the blunt cannula was also moved in-and-out to penetrate into different tracks in order to provide a comprehensive release of adhesive soft tissue. Finally, this cannula could sweep around the epicondyle area freely (for an angle about 30 degrees) with no resistance since all adhesive tissues had been released. Then this procedure was completed.

During this procedure, bleeding up to 10 mL occurred in one case due to injury to a small vein. However, it could be controlled easily immediately after the procedure. In average, the total blood loss during this procedure was less than 3 mL.

2.3. Outcome Assessment. Assessments of pain intensity, pressure pain threshold, and grasping strength were performed before, immediately after, 3 months after, and 12 months after the needle treatment (Figure 3).

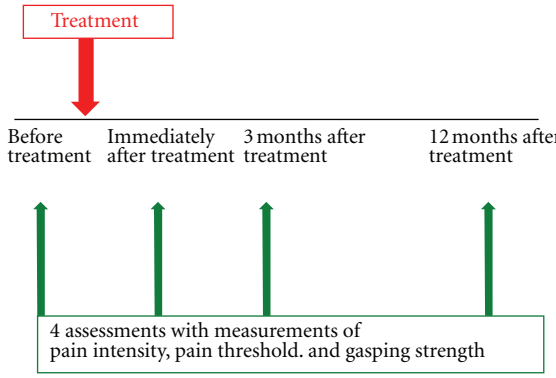

Figure 3: Schedule for outcome assessment.

2.3.1. Subjective Assessment of the Subjective Pain Intensity. The pain intensity over the elbow and forearm of the involved upper limb was assessed based on patient's subjective feeling before, immediately after, and 3 and 12 months after the treatment. It was subjectively reported by the patient using a "Numerical Pain Rating Scale" from zero to ten, with zero (0/10) representing no pain and ten (10/10) representing the worst imaginable pain. The patient was also informed that a value of pain intensity below 5/10 was considered as tolerable pain.

2.3.2. Assessment of the Pressure Pain Threshold. The pressure pain threshold at tender site of the lateral epicondyle was assessed on every subject before, immediately after, and 3 and 12 months after treatment. The procedure of measurement of the pressure pain threshold recommended by Fischer [26, 27] was applied in this study. The patient was in a comfortable sitting position and was encouraged to maintain complete relaxation. The procedure was explained to the patient clearly. Then the most painful spot in the lateral epicondyle was marked for 3 consecutive measurements so that 3 measurements could be performed over the same area. A pressure algometer (pressure pain threshold meter) was used to measure the pressure pain threshold. This pressure algometer was applied on this marked area with the metal rod perpendicular to the surface of the skin.

Table 2: Changes in subjective pain intensity.

Case	Before treatment	Immediately after treatment	3 month after treatment	12 months after treatment
A	8	2	0	0
B	9	1	0	0
C	7	0	1	0
D	8	1	0	0
E	9	2	0	0
F	7	0	0	0
Average	8.0 ± 0.9	1.0 ± 0.9	0.2 ± 0.4	0.0 ± 0.0
P value		<0.01	<0.01	<0.01

Table 3: Changes in pressure pain threshold (kg/cm^2).

Case	Before treatment	Immediately after treatment	3 month after treatment	12 months after treatment
A	2.2	3.6	4.0	3.8
B	1.7	3.3	4.2	4.3
C	2.3	2.9	3.9	4.2
D	2.0	2.8	4.1	4.0
E	1.9	3.1	4.2	4.1
F	2.2	3.5	3.3	3.7
Average	2.1 ± 0.2	3.2 ± 0.3	4.0 ± 0.3	4.0 ± 0.2
P value		<0.01	<0.01	<0.01

The pressure of compression was increased gradually at a speed approximately 1 kg/sec. The patient was asked to report any distinct increase of pain or discomfort. The compression stopped as soon as the subject reported that and the reading on the algometer was recorded as a value of pressure pain threshold. The patient was asked to remember this level of pain or discomfort at that point and to apply the same criterion for the next measurement. The patient might demonstrate pain by pulling away or grimacing, which indicated that the pain threshold had been exceeded [26, 27]. If this was the case, the patient was given instructions again and a repeat measurement was taken to ensure that the "real" threshold was obtained. Three repetitive measurements at an interval of 60 seconds were performed at each site. The average values of the three 3 readings (kg/cm^2) were used for data analysis. One well-trained examiner performed this measurement on all subjects at different times. For the initial assessment, this procedure was performed before and shortly after the needle treatment.

For every patient, the same measurement was performed over the most painful site of lateral epicondyle again 3 months and 12 months after the treatment. Every patient considered the most painful site was consistently the same one at different times.

2.3.3. Grasping Strength. Grasping strength is primarily measuring finger and hand flexors. However, when the extensors are painful during contraction, such as in the case of tennis elbow, the patient would have weakness in grasping strength since a fixation of wrist is very important to prove a powerful grasping. Ipsilateral hand grasping strength was measured with a hand dynamometer before, immediately after, and 3 and 12 months after treatment. The patient was requested to grasp the dynamometer using the maximal force of finger flexors against the dynamometer with the other end of the hand dynamometer fixed on the base of the palm. Three maximal efforts were tried for each assessment. The average of these 3 force values (kg) was used for data analysis.

2.4. Data Analysis. The measured data at different times after needle treatment were compared with the data before treatment based on the analysis of one-way ANOVA. A P value less than 0.01 was considered to be statistically significant.

3. Results

3.1. Changes in Subjective Pain Intensity. As shown in Table 2, the subjective pain intensity was remarkably reduced in every subject, with further improvement 3 and 12 months after treatment. In the follow-up study one year after the treatment, all subjects reported no pain. The changes in numerical rating scales were statistically significant ($P < 0.01$, Table 2).

3.2. Changes in Pressure Pain Threshold. Table 3 lists the changes in pressure pain threshold over tender spot of the lateral epicondyle before and after therapy. All subjects had remarkably increased pressure pain threshold immediately after therapy. Those effects lasted for up to 12 months. Statistically, those changes were statistically significant ($P < 0.01$, Table 3).

Table 4: Changes in strength of hand grasping.

Case	Before treatment	Immediately after treatment	3 month after treatment	12 months after treatment
A	8.1	22.1	27.6	31.2
B	5.3	14.5	18.8	18.4
C	7.8	15.4	22.7	21.0
D	12.7	26.9	27.6	38.1
E	9.3	22.2	31.0	31.2
F	8.8	21.1	23.1	24.2
Average	8.7 ± 2.4	20.4 ± 4.7	25.1 ± 4.4	27.4 ± 7.4
P value		<0.01	<0.01	<0.01

3.3. Changes in Grasping Strength. Similar to the improvement in subjective pain intensity and pressure pain threshold, the grasping strength of the involved hand had also been remarkably improved in all subjects, and those effects lasted for up to 12 months. All those changes were statistically significant ($P < 0.01$, Table 4).

4. Discussion

4.1. Summary of Important Finding in This Study. This pilot study demonstrated reduced subjective pain intensity, increased pressure pain threshold at the painful site, and increased grasping strength of the involved hand immediately after percutaneous soft tissue release over the lateral epicondylar region of the elbow in treating chronic myofascial pain of the forearm related to lateral epicondylitis. This effectiveness lasted for a period up to one year after treatment.

4.2. Correlation of Forearm Myofascial Pain and Lateral Epicondylitis. There have been evidences of the association between active MTrPs and lesions of nonmuscular origins, such as osteoarthritis of knee [28], cervical disc lesion [29], or cervical facet lesion [30]. Chiropractic adjustment [31] or local injection [32] of cervical facet joint could inactivate the MTrPs in the upper trapezius muscles. Bogduk and Simons [30] have suggested the possible connection between facet nociceptors and MTrP nociceptors in the spinal cord and a common use of nociceptive pathway to the higher center from these two kinds of nociceptors. Therefore, when the pain in the facet pain joint is suppressed, the pain due to MTrP can also be controlled, and vice versa. However, in our clinical practice or in searching for the literature, we could not find any case of cervical facet joint pain completely controlled with an MTrP injection of the upper trapezius muscle. On the other hand, facet injection can inactivate the MTrP in the upper trapezius muscle for a long period. Furthermore, if the pain in the upper trapezius MTrP is not elicited by the cervical facet lesion, the pain relief at the MTrP region should not last too long after the facet joint injection. In fact, the long-term relief of an MTrP pain could be observed in this study (longer than one year) and in a previous case report (longer than one year) [33]. Therefore, facet dysfunction may be one of the important causes to activate remote MTrPs. Our current study has further supported the importance of treating the underlying etiological lesion for long-term relief of myofascial pain due to MTrPs [6, 10].

4.3. Possible Mechanism of Pain Relief after Percutaneous Soft Tissue Release over the Epicondyle Region. The adhesion of soft tissues in the lateral epicondyle may be due to fibrosis in chronic inflammation. This chronic inflammation may be caused by direct tendon trauma (either acute pull or chronic repetitive minor trauma). The tendon lesion can activate the MTrP of the hand extensors whose common tendon is coming from the lateral epicondyle [3, 7]. The tendon trauma can be further aggravated by the tension of the taut band related to the MTrP of the hand extensor muscles. This can elicit a vicious cycle of elbow and forearm pain. Furthermore, it is very likely that the adhesion site contains attachment trigger points [4] that can be caused by the chronic tension produced by the taut band of that MTrP. The adhesion in the attachment trigger point region may further activate the MTrP of hand extensors (central sensitization). This condition can elicit another vicious cycle or enhance the whole vicious cycle (Figure 4). Therefore, when the adhesive tissue is released, the whole vicious cycle can be interrupted. Release of adhesive tissues with Lin's technique can provide either direct relief of adhesion or anti-inflammation (injection of local steroid). There the vicious cycle due to either adhesion or inflammation can be interrupted.

In this study, we also found an immediate relief of pain after the release of soft tissue. Theoretically, the anti-inflammatory effect from local steroid injection is not an immediate process. The immediate pain relief may be related to "hyperstimulation analgesia" from the needle stimulation, similar to MTrP injection or acupuncture [6, 10, 34]. Strong stimuli to nociceptors may elicit strong neural impulses to the spinal cord interneurons, including the hypothetic "MTrP circuit" of an MTrP [6, 10], to inhibit the vicious cycle of pain, and thus provide an immediate pain relief. Therefore, in addition to the adhesion release and anti-inflammatory effect, this procedure may also provide a hyperstimulation analgesic effect.

However, recent studies have suggested the noninflammatory nature of tendinopathy [35, 36]. It has been considered that lateral epicondylitis of elbow does not involve an inflammatory process of the common extensor

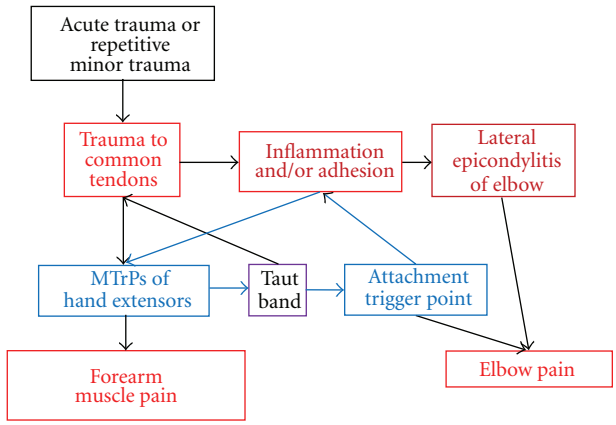

Figure 4: Vicious cycle of elbow and forearm pain.

origin (CEO). Kraushaar and Nirschl [11] proposed that the pathology is angiofibroblastic hyperplasia of the CEO [37]. Angiofibroblastic hyperplasia can cause soft tissue adhesion and elicit elbow pain. Therefore, surgical tenotomy has been suggested to treat elbow pain due to lateral epicondylitis by excision of the area of angiofibroblastic hyperplasia [12, 17]. Recently, percutaneous release of common extensor tendons at the lateral epicondyle [18–23] has become a popular procedure for treating lateral epicondylitis similar to surgical tenotomy. In fact, Lin's technique of release is one type of tenotomy similar to the procedure performed with percutaneous release of common extensor tendons at the lateral epicondyle [18–23]. However, recent studies have suggested that successful management of tendinopathy does not relate to excision of the actual tendinopathic lesion [38–40].

4.4. Technique Issues. The open approach of surgical tenotomy can provide a good visualization of the operative field and allows dealing with concomitant pathologies in the elbow [41, 42]. However, it is associated with increased failure rates and complications [41, 43]. It also produces increased time to return to the preinjury level of activity comparing to the procedure of percutaneous techniques [21].

The percutaneous technique had a lower complication rate than the open approach of surgical tenotomy [18, 20, 22, 44]. It can be performed as an office procedure. The procedure of Lin's technique is actually a procedure of percutaneous release of adhesion as previously performed by orthopedic surgeon with a knife or a 18 K needle [23]. The major difference between these two procedures is that a blunt cannula instead of a sharp knife or needle is used in this new procedure. Using this new procedure, the recovery period can be much shortened, and the patient has less suffering.

4.5. Limitation of This Study. The major limitation of this study included the small sample sized and the lack of control group. Since this is just a pilot case study, we plan to have further control study on patients of a bigger sample size in the near future.

5. Conclusion

This pilot study indicated therapeutic effectiveness of percutaneous soft tissue release in treating chronic myofascial pain of the forearm related to lateral epicondylitis. Since it is much less invasive than other surgical procedures, this technique can be recommended for the treatment of recurrent lateral epicondylitis with myofascial pain of the forearm muscles with poor responses to conservative treatment (such as oral medicine, physical therapy, or local steroid injection).

Author's Contribution

L.-W. Chou had provided the same effort as M.-T. Lin.

Disclosure

No commercial party having a direct financial interest in the results of the research supporting this paper has or will confer a benefit upon the authors or upon any organization with which the authors are associated.

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