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Application of an artificial neural network model for early outcome prediction of gamma knife radiosurgery in patients with trigeminal neuralgia and determining the relative importance of risk factors

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ABSTRACT

Objectives: Stereotactic radiosurgery (SRS) is a minimally invasive modality for the treatment of trigeminal neuralgia (TN). Outcome prediction of this modality is very important for proper case selection. The aim of this study was to create artificial neural networks (ANN) to predict the clinical outcomes after gamma knife radiosurgery (GKRS) in patients with TN, based on preoperative clinical factors.

Patients and methods: We used the clinical findings of 155 patients who were underwent GKRS (from March 2000 to march 2015) at Iran Gamma Knife center, Teheran, Iran. Univariate analysis was performed for a long list of risk factors, and those with P-Value < 0.2 were used to create back-propagation ANN models to predict pain reduction and hypoesthesia after GKRS. Pain reduction was defined as BNI score 3a or lower and hypoesthesia was defined as BNI score 3 or 4.

Results: Typical trigeminal neuralgia (TTN) (P-Value = 0.018) and age > 65 (P-Value = 0.040) were significantly associated with successful pain reduction and three other variables including radiation dosage > 85 (P-Value = 0.098), negative history of diabetes mellitus (P-Value = 0.133) and depression (P-Value = 0.190). On the other hand, radio dosage > 85 (P-Value = 0.008) was significantly associated with hypoesthesia, other related risk factors (with p-Value < 0.2), were history of multiple sclerosis (P-Value = 0.106), pain duration more than 10 years before GKRS (P-Value = 0.115), history of depression (P-Value = 0.139), history of percutaneous ablative procedures (P-Value = 0.148) and history of diabetes mellitus (P-Value = 0.169).ANN models could predict pain reduction and hypoesthesia with the accuracy of 84.5% and 91.5% respectively. By mutual elimination of each factor in this model we could also evaluate the contribution of each factor in the predictive performance of ANN.

Conclusions: The findings show that artificial neural networks can predict post operative outcomes in patients who underwent GKRS with a high level of accuracy. Also the contribution of each factor in the prediction of outcomes can be determined using the trained network.

1. Introduction

Trigeminal neuralgia is a rare debilitating pain condition, characterized by unilateral recurrent paroxysmal lancinating pain, that is confined to the distribution of 1 or more branches of trigeminal nerve and magnified by cutaneous perturbations [1].With an incidence ranging from less than 5 to 28.9 per 100,000 according to different studies, women are more commonly affected than men and there is a progressive increase of the incidence with age [2–5]. According to clinical patterns trigeminal neuralgia has been classified as typical (TTN) (TN1) or atypical (ATN) (TN2). TN1 is defined as short attacks of intense stabbing pain as a response to definite triggers whereas TN2 is described as burning or aching pain which is present in more than 50% of the time of the day [6,7].

The first line therapy is medical management [8].Although many patients respond to medical therapy, other treatments for medication-refractory patients include microvascular decompression (MVD), percutaneous ablative procedures using physical, thermal or chemical agents and also stereotactic radio surgery (SRS) [9–11]. Radio surgery which was invented by the Swedish neurosurgeon Lars Leksell [12] has became increasingly popular for the treating of trigeminal neuralgia not only due to its non- invasive nature, but also because of its simplicity

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and reasonable risk to benefit profile [13–15].

Multiple prognostic factors have been studied to predict better response or complication rates after SRS [16–22,42].

Artificial neural networks are mathematical models for non linear information processing which are composed of highly interconnected groups of processing elements (artificial neurons or nodes). They can be used to solve specific problems with complex relationships between given inputs and sought-after outputs, via a learning process. So by estimating the input/output relationships, they can predict outcomes for given inputs [23].In medical fields, ANN models have been used in accurate diagnosis, classification, pattern recognition and outcome prediction [24,25]

To our knowledge, relationships between predictive risk factors and outcomes of GKRS in treatment of TN have not been previously investigated using the artificial neural network (ANN) model.

2. Material and methods

2.1. Patients

After approving by the institutional Ethical committee of Tehran University of medical sciences and Iran Gamma knife center, we performed a single-center retrospective review of registered data-base for patients with trigeminal neuralgia who underwent SRS at the Iran Gamma knife center between 2000 and 2015. This study was carried out in accordance with the declaration of Helsinki.

Post operative datasets including pain status and hypoesthesia were collected by follow up records that were routinely performed at least 6 months after the operation. The follow up range were between 6 and 23 months with the mean period of 13.2. On occasion telephone interviews were conducted to retain the missing data.

Pre operative and post operative pain status were recorded based on Borrow Neurological Institute (BNI) score for trigeminal neuralgia. A BNI 1 score corresponded to complete pain relief without medications; BNI 2 score, occasional pain but not requiring medications; BNI 3a score, no pain with medications; BNI 3b score, persistent pain but adequately controlled with medications; BNI 4 score, some pain not adequately controlled with medications; and BNI 5 score, severe pain or no pain relief [26].

The degree of post operative hypoesthesia was reported using the BNI hypoesthesia scale. BNI 1 score, corresponds to no facial numbness; BNI 2 score, mild facial numbness, not bothersome; BNI 3 score facial numbness, somewhat bothersome; and BNI 4 score, facial numbness, very bothersome [26].

The quality of trigeminal pain was evaluated according to the classification proposed by Eller et al comprising TN1 and TN2. Typically sharp, shooting, electrical shock like pain with pain free intervals that is present for more than 50% of time described as TN1, and TN2 is characterized by an aching, throbbing or burning pain which is constant in nature and presents for more than 50% of time [6].

The patients with facial pain of BNI grade 3 or 4 which was refractory to medical and/or surgical managements, who underwent SRS for the first time, were included in this study. We excluded cases with facial pain, caused by intracranial mass lesions. Other exclusion criteria were BNI pain score = < 3, lack of qualified medical data and repeat SRS. Successful pain control was defined as a BNI score 1 – 3a. Post operative hypoesthesia was defined as BNI score 3 or 4 which has been occurred after radiosurgery.

2.2. Radiation surgery technique

Gamma knife radiosurgery was performed using the model C Leksell gamma knife; (Elekta instruments, Stockholm, Sweden). High resolution magnetic resonance imaging with and without contrast and computed tomography were performed after application of the Leksell stereotactic frame (Elekta instruments) under light sedation. A single 4 mm isocenter was typically positioned 2–4 mm anterior to the junction of the trigeminal nerve and the pons, such that the brain stem surface was irradiated at the 50% isodose line with doses not more than 22 Gy. Treatment planning was performed by a team consisting of a neurosurgeon, radiation oncologist, and medical physist, using the Leksell Gammaplan software. The prescription dose to the 100% isodose line was from 60 to 98 Gy and was not chosen based on patient factors.

2.3. Statistical analysis

For the first part we conducted a univariate analysis of several variables, hypothesized to predict post operative outcomes (successful pain reduction or clinically significant hypoesthesia) using SPSS software package version 23. The comparison made via chi-square testing. The P-value of less than 0.05 was considered statistically significant and variables with P-value of less than 0.2 in the univariate analysis were used to develop Artificial Neural Network models.

In the second part, two artificial neural networks were designed by the software MATLAB R2013b (MathWorks,Inc,MA-USA).The first model, was constructed to predict pain reduction and the second to predict hypoesthesia. For model construction, we selected MLP (multi layer perceptron) neural networks with backpropagation training algorithms. This model is one of the most popular network architectures currently in use [27].

Each MLP consists of three layers: input layer, hidden layer and output (target) layer. Prognostic factors - which were those with P-Value < 0.2 in univariate analysis - were used as input layers. Output or target layers were pain reduction in the first model and hypoesthesia in the second model. First network (for predicting pain reduction) consisted of 19 nodes in hidden layer and the second network (for predicting hypoesthesia) had 14 nodes in the hidden layer. The numbers of hidden nodes were determined via trial-and-error procedures with a changing number of hidden nodes to select the structure with the best performance. Gradient descent was performed to estimate the synaptic weights. MSE (mean squared error) was used as network performance function.

3. Results

3.1. Participants and descriptive data

Patient demographics and presentations are shown in Table 1. The median age of the patients was 56 years (range;18–91). 47 (30.3%) of them were above 65 years and the rest 108 (69.7%) patients were under 65. There were 83 (53.5%) men and 72 (46.5%) women.

The pain was on the right side in 87 (56.1%) and on the left side in 64 (41.3%) patients. 4 (2.6%) patients had bilateral pain.

133 (85.5%) of patients had typical form of trigeminal neuralgia (TN1), and 22 (14.2%) had atypical form (TN2) according to Eller classification [6]. 8 (5.2%) patients had multiple sclerosis disease. 30 (10.4%) patients were hypertensive. Diabetes mellitus was diagnosed in 12 (7.7%) patients, and 9 (5.8%) patients had depression which had been diagnosed by psychiatrist and was under medical treatment. Median time passed from the onset of disease and radio surgery was 6.7 years (range; 1-30y). Patients were treated with the maximum dose of 60–98 Gy (mean 82.6). 23 (14.9%) patients had prior surgical procedures, which consisted of microvascular decompression in 17 (11%) and percutaneous ablative techniques in 6 (3.9%) patients.

3.2. Prognosticators

In the primary univariate analysis, only two variables were significantly correlated to successful pain reduction. These variables were the type of trigeminal neuralgia (TN1 Vs TN2) (P-Value = 0.018) and the age of patients (> 65y Vs < 65y) (P-Value = 0.040).Three other

Table 1
Patient demographics and presentations.

Characteristic	Value
Gender	
Male	83 (53.5%)
Female	72 (46.5%)
Mean age (range)	56.29 (18-91)
Median duration in years (range)	6.72 (1-30)
Side of pain	
Right	87 (56%)
Left	64 (41.3%)
Both sides	4 (2.6%)
Pain distribution	
V1	2 (1.3%)
V2	50 (38.1%)
V3	20 (12.9%)
V1 + V2	14 (9%)
V2 + V3	42 (30.3%)
V1 + V2 + V3	13 (8.4%)
Type of pain	
TN1	133 (85.5%)
TN2	22 (14.2%)
PAST MEDICAL HISTORY	
Depression	9 (5.8%)
Hypertension	30 (19.4%)
Diabetes mellitus	12 (7.7%)
Multiple sclerosis	8 (5.2%)

variables were correlated to pain reduction, but not statistically significant. Dosage of radiosurgery (> 85) (P-Value = 0.098) was associated with higher pain reduction, negative correlations were seen between the history of diabetes mellitus (P-Value = 0.133) and history of depression (P-Value = 0.191) with pain reduction rates.

Higher radiosurgery dosage (> 85) (P-Value = 0.008) was significantly correlated to post operative hypoesthesia. But history of multiple sclerosis (P-Value = 0.106), long duration of neuralgia (> 10y) (P-Value = 0.115) before radiosurgery, history of depression (P-Value = 0.139), history of precutaneous ablative techniques (P-Value = 0.148) and history of diabetes mellitus (P-Value = 0.169) were associated with higher rates of post operative hypoesthesia, but not statistically significant.

3.3. Artificial neural network model

In this study, two multi layer perceptron (MLP) networks conducted as standard feed-forward back propagation neural networks, were designed to predict pain reduction and hypoesthesia. The data of 155 patients were randomly divided into a training sample of 108 cases (70%) and a test sample of 47 (30%) cases.

3.4. ANN for prediction of pain reduction and assessments of prognostic factors

To predict pain reduction, we used the following variables as inputs: type of trigeminal neuralgia (TN1 or TN2), age of patients (> 65y or < 65y), dosage of radiosurgery (> 85 or < 85), history of diabetes mellitus and history of depression. The best results were made by a network consisted of 19 nodes in the hidden layer. The network could predict successful pain reduction for the test dataset and the whole dataset with the accuracy of 91.5% and 84.5% respectively. The final MSE was 0.212. Fig. 1 shows the confusion matrices for each dataset. The numbers of correct and incorrect predictions compared to actual outcomes were shown.

To find the relative importance of each variable in accurate outcome prediction, we performed the networks with the same structures and the same dataset, but used only 4 variables as input nodes instead of five, once deleting each of the five input variables in turn. We calculated the accuracy of pain reduction predictions in these new networks.

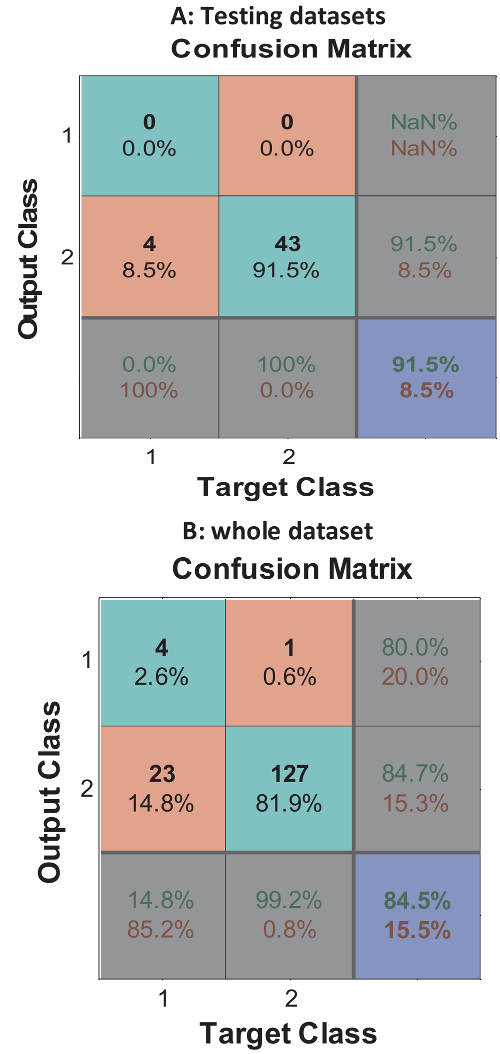

Fig. 1. The confusion matrices showing the number of correct and incorrect predictions of pain reduction made by each set of data using testing datasets (a) and whole dataset (b).

So for each time a new network with 4 input variables, 19 hidden nodes and the same setting characters like the original network was developed. The more drop in the prediction accuracy of the network means the more importance of the deleted variable. Based on this rational, as shown in Table 2 the age more than 65, had the most contribution in the network prediction performance in our dataset. In descending order, the other effective variables were: pain type, radiosurgery dosage, history of depression and history of diabetes mellitus.

Table 2
The accuracy of the trained network by deleting each of input variables to predict pain reduction.

Ranking in the predictive performance	deleted variable	new network accuracy
1	age > 70 y	78.7%
2	pain type	83%
3	Radiation dose	83.9%
4	Depression	85.1%
5	Diabetes mellitus	87.2%

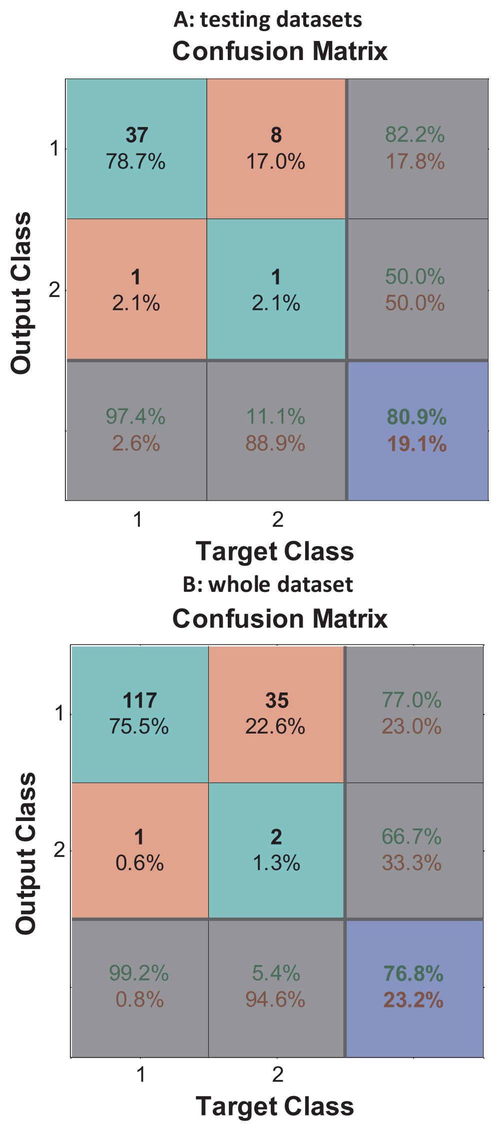

Fig. 2. The confusion matrices showing the number of correct and incorrect predictions of hypoesthesia made by each set of data using testing datasets (A) and whole dataset (B).

3.5. ANN for prediction of hypoesthesia and assessments of prognostic factors

To predict hypoesthesia, a three layer MLP with 14 hidden nodes were developed with the following 6 variables in the input layer: radio dosage, history of percutaneous ablative techniques, pain duration before radiosurgery more than 10 years, history of diabetes mellitus, multiple sclerosis and depression. The accuracy of prediction were 80.9% for the test dataset and 76.8% for the whole dataset as shown in the Fig. 2 with final MSE = 0.240.

By mutually deleting each of input variables, we found more reduction in the prediction accuracy of the network by deleting radio dosage variable, which were considered the most contributed factor to predict hypoesthesia in our dataset. Table 3 shows the accuracy of new networks by deleting each variable.

4. Discussion

Trigeminal neuralgia ranks among the most painful conditions known to mankind and has been named as the suicide disease in some old literatures, because of its bothersome course and poor outcome [28].

Table 3
The accuracy of the trained network by deleting each of input variables to predict hypoesthesia.

Ranking in the predictive performance	deleted variable	new network accuracy
1	radiation dosage	72.3%
2	percutaneous procedures, pain duration > 10 y	76.6%
3	diabetes mellitus Multiple sclerosis Depression	78.7%

SRS represents the least invasive modality for the treatment of TGN and achieves acceptable pain relief in properly selected patients, so it has been increasingly selected as primary intervention for appropriate patients over the last two decades [29,30].

So many attempts have been done to clarify the prognostic factors for prediction desirable outcomes and potentially complications using this modality, but the available data in the literature are controversial and confusing.

Although several studies have indicated TN2 to be a predictor of poor response to SRS, [14,19,31–33], some other studies, showed no significant differences between TN1 and TN2 in favorable outcomes [22,34,35].

Zachary *J.* Taich et al showed that age > 70, radio dosage > 90, TN1 and prior percutaneous procedures, were significantly correlated with better outcomes. On the other hand, radiation dose of 90 and prior SRS, significantly increased post operative facial numbness. History of MS was not a poor prognostic factor in their series [21].

Although Brisman R has reported that patients with MS are less likely to respond to SRS than patients without MS [36], this issue was not suggested by several other studies [21,34,37].

Age > 70 was predictive of better pain relief in several studies, such as those reported by Andrew M.Bashnagel et al [34], Han et al [38] and Sana D.Karam et al [39], but Flickinger JC et al have reported the correlation between pain relief and younger age [40].

In another paper published by Sana D.Karam et al diabetic status of the patients was shown to be a negative prognostic factor [41].

Analysis of the series of Marshall K et al, revealed that decreased efficacy of SRS is associated with prior radiofrequency ablation and diabetes mellitus status [42].

Given the complex nature of this disease, many subtle factors, may easily be missed or go unrecognized. Positive or negative outcomes can be influenced by several factors which have nonlinear relationships between each other and the associated outcomes. So, standard linear regression models might be useless for outcome predictions in such complicated topics. It has been suggested that ANN is more useful to predict clinical outcomes than conventional statistics techniques, when there are complex and poorly understood relationships between independent variables and clinical outcomes [43–45].

The application of ANNs in medical fields backed to the late 1980s. Especially they have been used for accurate diagnosis, determination of disease severity and outcome predictions [24,46].

Although the ANN was established before the advent of computer [47], computational models based on relevant mathematics and algorithms, lead to abrupt application of this technique in several eras. Indeed, the ability of computers to gather and process thousands of variables, made them capable to be trained by simulated "trial-and-error" processing, so computers can learn to recognize patterns and make informed decisions. This technology is often called "artificial intelligence" and is already in use in different fields of technology and also in certain areas of medicine [23,48].

Nowadays, application of these new technologies in routine clinical use becomes easier than past by increasing availability of computer based techniques and electronic medical information.

These techniques can help the clinicians to make more accurate diagnosis and select the most appropriate treatment modality, based on the prognostic factors of each patient individually [49–51].

In the current study, we revealed that the artificial neural network can be used for outcome prediction in patients with trigeminal neuralgia who were underwent stereotactic radiosurgery and also it can be used to find the relative importance of each risk factor.

5. Limitations

This study is subject of important limitations. Because of retrospective methodology we had access only to the short term outcomes, so in future we try to re-collect the long term outcomes with longer follow up periods.

The other important limitation was small sample size so we could not find the hidden risk factors by using ANN, so at this stage we focused on known risk factors to find the relative importance of each of them by using artificial neural network.

Other limitations were presented by conducting a single center study; small sample size and a uniform technique of radiosurgery. So comparison of different technical issues were impossible

To overcome these problems and generation of more robust results, we suggest multi center collaborations to increase the power of such studies.

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