European Annals of Otorhinolaryngology, Head and Neck diseases 136 (2019) 251–255

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Original article

Therapeutic effect of pregabalin on radiotherapy-induced trismus in nasopharyngeal carcinoma patients

H. Li [a], Q. Yao [b], X. Huang [a], X. Zhuo [a], J. Lin [a], Y. Tang [a,c,d,*]

[a] Department of Neurology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, 510120 Guangzhou, China
[b] Department of Neurology, Quanzhou First Hospital Affiliated to Fujian Medical University, Quanzhou, Fujian-Province, China
[c] Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China
[d] Guangdong Province Key Laboratory of Brain Function and Disease, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, China

INFO ARTICLE

Keywords :
Radiotherapy-induced trismus
Pregabalin
Mandibular motion
Quality of life
Clinical study

ABSTRACT

Aims. – To evaluate the effect of pregabalin on radiotherapy-induced trismus in patients with nasopharyngeal carcinoma, a hospital-based, clinical retrospective cohort study was conducted.
Materials and methods. – Data were collected on patients diagnosed with radiotherapy-induced trismus from March 2014 and March 2016 in the department of neurology in our hospital. Patients in the treatment group were administrated pregabalin for 8 weeks combined with rehabilitation, while the control group only received rehabilitation. The clinical therapeutic effects were observed and evaluated by mandibular motion, severity of trismus measured by late effects of normal tissues/subjective and objective medical analysis (LENT/SOMA) scales, and quality of life (QOL) assessed using the World Health Organization QOL instrument (WHOQOL-BREF) at baseline, week 4 and week 8 during treatment in these two groups, respectively.
Results. – In the treatment group, the number of patients with improvement on maximal vertical dimension (MVD) was significantly more than controls at week 4 and week 8 ($P = 0.013$, $P = 0.004$, respectively). Moreover, at week 4 and week 8, the severity of trismus was both significantly improved on LENT/SOMA grade in treatment group ($P = 0.047$, $P = 0.032$, respectively). And at week 8, the physical health and the whole life domain of the WHOQOL-BREF score were significantly increased ($P = 0.037$, $P = 0.034$, respectively). In the treatment group, 11 patients (36.7%) presented dizziness, and 7 patients (23.3%) presented somnolence.
Conclusions. – Administration of pregabalin, in adjunct to rehabilitation, might provide a better outcome in patients with radiotherapy-induced trismus.

1. Introduction

Trismus was initially described in the setting of tetanus, which currently refers to restricted mouth opening due to any etiology. It is well known that radiotherapy-induced trismus is one of the most common and severe complications following radiotherapy [1,2]. The prevalence of trismus after head and neck oncology treatment ranged from 5% to 38% [3]. Radiotherapy induces fibrosis in the mastication muscles and necrosis of bone and soft tissue which restricts the mouth opening [4]. Trismus may contribute to eating and speech difficulties, impaired oral hygiene, and altered facial expression [5]. Additionally, trismus may interfere with appropriated oral intake of nutrition and hydration, and even cause aspiration due to impaired swallowing function that negatively influence patients' quality of life [6,7]. However, few treatments have been proved to be efficient for radiotherapy-induced trismus [8–10].

Pregabalin is derived from gamma-aminobutyric acid (GABA) that exerts its anticonvulsant activity through binding to alpha 2 delta 1 auxiliary subunit of the voltage-gated Ca^{2+} channel [11]. Pregabalin has received FDA approval for patients with central neuropathic pain, partial seizures, generalized anxiety disorder, fibromyalgia and sleep disorders [12]. It has been reported that pregabalin can reduce the smooth muscle vasoconstriction and spasm [13].

We carried out this retrospective study to evaluate the efficacy and safety of pregabalin on radiotherapy-induced trismus in patients with nasopharyngeal carcinoma (NPC).

* Corresponding author at: Department of Neurology, Sun Yat-Sen Memorial Hospital, Sun Yat-sen University, 107, Yan-Jiang-Xi Road, 510120 Guangzhou, China.
Adresse e-mail : yameitang@hotmail.com (Y. Tang).

https://doi.org/10.1016/j.anorl.2018.10.018

Table 1
Demographic data of patients in two groups.

	Tret.	Con.	*P* value
No.	30	28	
Male	20 (66.7%)	18 (64.3%)	0.326[a]
Age (year)	50 ± 8	54 ± 9	0.227[b]
Clinical latency (month)	48 ± 14	41 ± 18	0.252[b]
Radiation dose (Gy)	77 ± 22	72 ± 14	0.532[b]
MVD (mm)	19 ± 5	20 ± 5	0.696[b]

Tret.: treatment group; Con.: control group; No.: number; MVD: maximal vertical dimension.
[a] Chi^2 test.
[b] Mann–Whitney test.

2. Materials and methods

This hospital-based, clinical retrospective cohort study, was approved by an authorized human research review board in our institute. The appropriate ethical committee has formally approved the experiments. The study was conducted with the understanding and the written consent of each participant.

Between March 2014 and March 2016, patients who fulfilled the following eligibility criteria were included for analysis:

- a history of NPC with radiotherapy;
- trismus occurred after radiation therapy;
- no evidence of trismus because of primary oral and temporomandibular joint disease;
- age ≥ 18 years;
- patients who have received rehabilitation treatment only or combined with pregabalin.

Patients were excluded from analysis if they were diagnosed with tumor recurrence or metastases. To reduce the selection bias of our study, subjects were recruited from different sources, including inpatients and outpatients. Sixty-four patients with radiotherapy-induced trismus were scanned. However, 2 patients were diagnosed with NPC recurrence, 2 patients were diagnosed with neck metastases, 2 patients had trismus before RT because of temporo-mandibular disorders. Thus, a total of 58 patients was included in this study, including 30 patients treated by rehabilitation treatment combined with pregabalin, and 28 patients treated by rehabilitation treatment only.

The 58 patients included 38 men and 20 women, whose age varied from 22 to 85 years. The mean age was 50 ± 8 in treatment group and 54 ± 9 in control group. The demographic and clinical data of patients in two groups are in Table 1. There was no statistical difference between treatment group and control group regarding age, gender, clinical latency, radiation dose, the severity of trismus at baseline ($P > 0.05$).

In this study, we compared the effects of pregabalin plus rehabilitation treatment versus rehabilitation treatment alone. The following treatments were conducted both in treatment group and control group:

- symptomatic support therapy, including the use of dehydrated drugs when tissue edema happened, and the use of antibiotics when infection happened;
- rehabilitation treatment, including physiotherapy, swallowing and trismus rehabilitation exercise.

Besides, pregabalin was conducted in the treatment group. The starting dose of pregabalin was 75mg by oral administration twice a day in the morning and evening respectively. Then, the dosage of 75mg would be added per week, until satisfying therapeutic effect was observed, or the adverse effects of the drug cannot be tolerated. The maximum therapeutic dose was 300mg/day, maintaining the stable dose until the 8 weeks of the total treatment. The diagnosis and treatment of trismus was based on clinical experience and good clinical practice, partly because no clear criteria have been established [3,14]. Three measurements in the following were used to evaluate the severity of trismus at baseline, week 4, week 8 during treatment.

Maximal vertical dimension (MVD) and the mandibular side motion were used to evaluate the severity of trismus [15,16]. MVD refers to the distance between incisors in the upper and lower incisors when the mouth is open. Mandibular side motion including left mandibular movement (LMM) and right mandibular movement (RMM) were measured. Calipers were used to measure all these data.

Late effects of normal tissues/subjective and objective medical analysis (LENT/SOMA) were also used to evaluate the severity of trismus [17]. Both the experimental group and the control group were scored by five assessment indicators according to the LENT/SOMA scale [18]. According to this standard, trismus was divided into the following 4 grades:

- grade 1, MVD was > 20mm, questionable changes or none in mandibular radiograph;
- grade 2, MVD was 11–20mm, has difficulty in eating solid foods, osteoporosis or osteosclerosis in mandibular radiograph;
- grade 3, MVD was 5–10mm, has difficulty in eating liquid foods, sequestra in mandibular radiograph;
- grade 4, MVD < 5mm, nasal feeding was necessary, fracture in mandibular radiograph (Table 2).

There is currently no consensus as to which treatment modality results in better outcomes [10]. The effective response was defined as improvement of MVD ≥ 1 grade of LENT/SOMA compared with baseline.

QOL was assessed using the World Health Organization QOL instrument (WHOQOL-BREF), which comprises 26 items and measures the following broad domains: physical health, psychological health, social relationships, and environment, whole health and whole life domain [19].

Table 2
LENT/SOMA scale of trismus.

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective	Noted but unmeasurable	Preventing normal eating	Difficulty eating	Inadequate oral intake
Objective	> 20 mm opening	11–20 mm opening	5–10 mm opening	< 5 mm opening
Management	Not available (NA)	Soft diet	Liquid diet, antibiotics, muscle relaxant meds	NG tube, gastrostomy
Analytic mandibular radiograph	Questionable changes or none	Osteoporosis, osteosclerosis	Sequestra	Fracture
Panograph X-rays/CT	Assessment of necrosis progression			

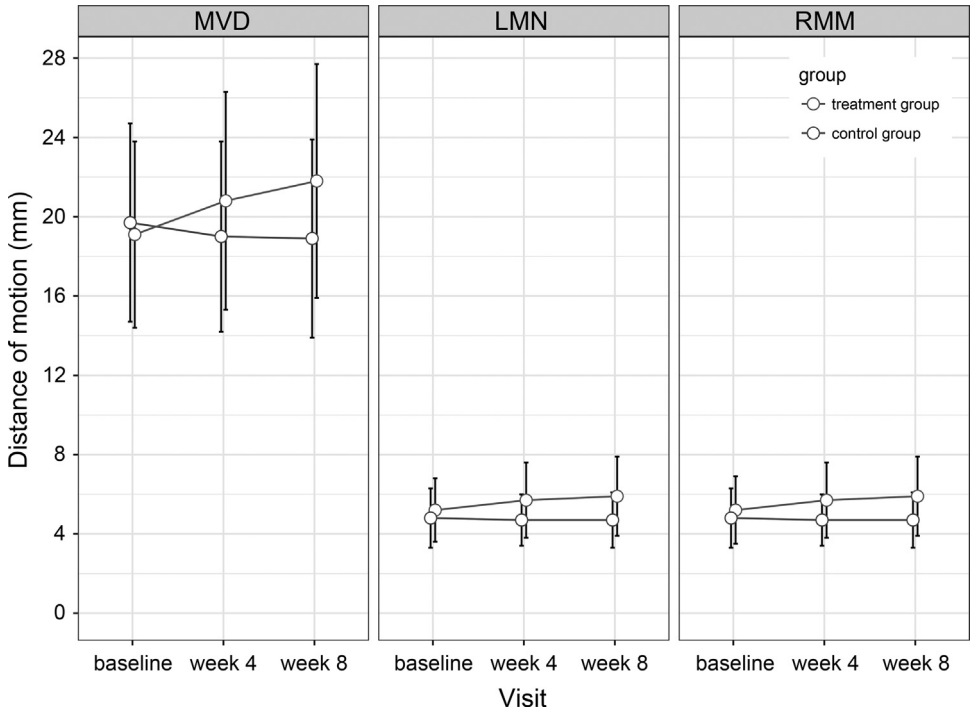

Fig. 1. Mandibular motion between two groups. No significant difference was observed regarding the MVD, LMN, and RMN ($P > 0.05$) both at week 4 and week 8. The mandibular motion between two groups were analyzed by Mann–Whitney U test.

Table 3
Number of patients with improvement on mandibular motion between two groups.

	Week 4 (*n*)		Week 8 (*n*)	
	Tret.	Con.	Tret.	Con.
MVD, mm	24	10	26	10
LMN, mm	23	16	23	16
RMM, mm	22	16	24	16

Tret.: treatment group; Con.: control group; MVD: maximal vertical dimension; LMM: left mandibular movement; RMM: right mandibular movement.
The therapeutic efficacies on mandibular motion between two groups were analyzed by Chi^2 test.

The SPSS 21.0 was used for data processing. The data are presented as mean (standard deviation), or number (%). Mann–Whitney U test was used in the comparison of age, clinical latency, radiation dose, MVD, LMN, and RMN data. The comparison of qualitative data between two groups such as gender, was performed using Chi^2 test. The therapeutic efficacies on LENT/SOMA grade between two groups were analyzed by Chi^2 test. The QOL scores between two groups were analyzed by One-way ANOVA S-N-K test. *P* value < 0.05 was used for statistical significance.

3. Results

MVD, LMN, RMN were measured at baseline, week 4 and week 8 during treatment to evaluate the mandibular motion. There was no statistical difference between these two groups regarding the MVD, LMN, and RMN (Fig. 1). But when Chi^2 test was used to compare the number of patients who received improvement after pregabalin treatment, this test showed that the number of cases with MVD improvement in the treatment group was significantly more than those in the control group both at week 4 ($P = 0.013$) and week 8 ($P = 0.004$) (Table 3). No difference was found on LMN and RMN ($P > 0.05$).

Moreover, LENT/SOMA scale was used to evaluate the severity of trismus at baseline, and week 4, week 8 during treatment. Chi^2 test was used in this analysis. At week 4, 15 of 30 (50.0%) patients in treatment group and 6 of 28 (21.4%) patients in control group received an effective response ($P = 0.047$) (Fig. 2). While at week 8, 18 of 30 (60.0%) patients in treatment group and 8 of 28 (28.6%) patients in control group received an effective response ($P = 0.032$) (Fig. 2).

The WHOQOL-BREF score was transformed into standard scores in line with the WHQOL-100 Instrument [20]. The higher the score, the better QOL the patients gained. Comparison of WHOQOL-BREF scores between two groups was presented in Table 4. The results showed no significant difference of all these scores between the treatment group and the control group at baseline. However, after 8 weeks treatment of pregabalin, patients in the treatment group got a significantly higher score in physical health (48.92 ± 10.44 vs. 43.81 ± 17.85, $P = 0.037$), and the whole life domain (2.91 ± 0.55 vs. 2.55 ± 0.41, $P = 0.034$) compared with that in the control group. Yet, no significant difference was found in social relationships, environment, and whole health domain of WHOQOL-BREF between two groups ($P > 0.05$). Dizziness was observed in 11 patients among 30 patients (36.7%) in treatment group. And 7 patients (23.3%) presented somnolence. No other serious side effects were found.

4. Discussion

Despite the high prevalence and personal and public health burden of radiotherapy-induced trismus, few clinical studies have evaluated therapies for trismus. In this study, we evaluated the therapeutic effect of pregabalin on radiotherapy-induced trismus in NPC patient. According to our findings, after pregabalin treatment, many patients got MVD improvement. Furthermore, treatment with pregabalin showed a more notable improvement in the severity of trismus assessed by LENT/SOMA grade, and the physical health and the whole life domain of WHOQOL-BREF were significantly increased in treatment group.

Moreover, at week 4 and week 8, the severity of trismus was significantly improved in treatment group ($P = 0.047$, $P = 0.032$,

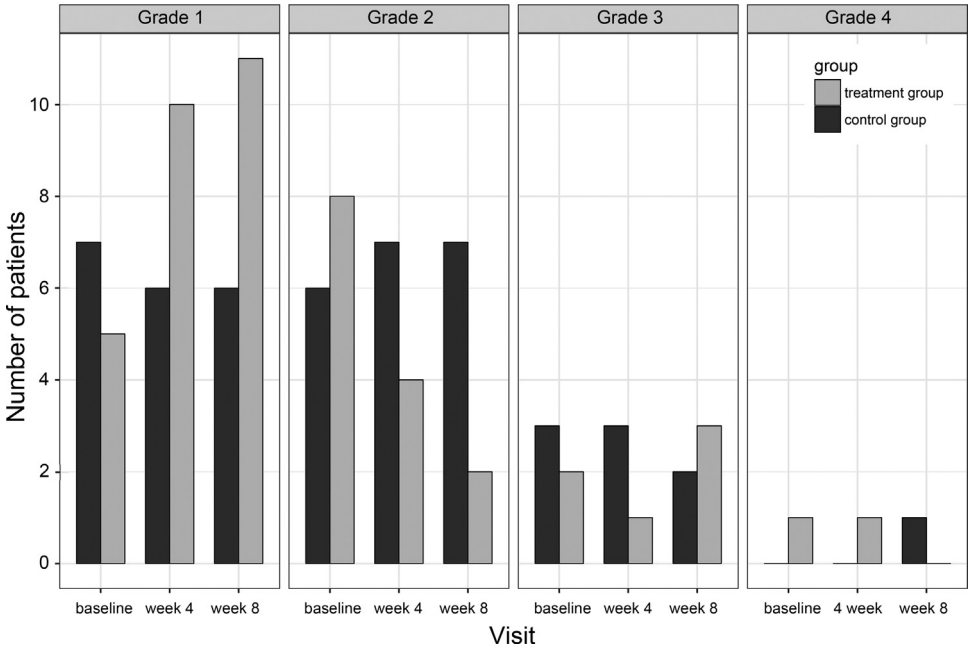

Fig. 2. The therapeutic efficacies on the LENT/SOMA grade between two groups. At week 4, 15 of 30 (50.0%) patients in treatment group and 6 of 28 (21.4%) patients in control group received an effective response ($P = 0.047$). While, at week 8, 18 of 30 (60.0%) patients in treatment group and 8 of 28 (28.6%) patients in control group received an effective response ($P = 0.032$). Analysis of Chi^2 test was conducted.

Table 4
WHOQOL-BREF scores between two groups.

	Physical health	Psychological health	Social relationships	Environment	Whole health	Whole life
Tret.						
BL.	42.38 ± 16.03	41.84 ± 12.59	45.97 ± 10.05	50.61 ± 13.19	1.37 ± 0.81	2.36 ± 0.49
Week 4	47.20 ± 17.82	43.62 ± 19.19	42.28 ± 15.87	51.60 ± 15.81	1.77 ± 0.58	2.61 ± 0.69
Week 8	48.92 ± 10.44	44.89 ± 14.40	45.07 ± 17.82	50.94 ± 14.56	2.03 ± 0.87	2.91 ± 0.55
Con.						
BL.	45.16 ± 11.87	41.33 ± 15.43	40.75 ± 11.06	54.16 ± 12.32	1.31 ± 0.83	2.33 ± 0.64
Week 4	45.67 ± 14.36	43.20 ± 12.70	43.95 ± 13.37	53.41 ± 15.72	1.46 ± 0.60	2.53 ± 0.47
Week 8	43.81 ± 17.85	48.01 ± 14.33	44.68 ± 11.71	54.82 ± 16.15	1.42 ± 0.64	2.55 ± 0.41

Tret.: treatment group; Con.: control group; BL.: baseline.
The WHOQOL-BREF scores between two groups were analyzed by One-way ANOVA S-N-K test.

respectively). And at week 8, the physical health and the whole life domain of the WHOQOL-BREF were significantly increased.

Pregabalin is derived from gamma-aminobutyric acid (GABA) that exerts its anticonvulsant activity through binding to alpha 2 delta 1 auxiliary subunit of the voltage-gated calcium channel. Then, it is effective to the spontaneous pain, hyperalgesia and hypersensitivity by reducing the release of glutamate, norepinephrine, P and other excitatory neurotransmitters [21]. Treatment of trismus is commonly treated symptomatically [14]. It has been noted that pregabalin, by elevating α2δ-1 expression, promotes surface trafficking of CaV1.2 channels and by reducing the in current inactivation in cerebral artery myocytes of hypertension mouse, can reduce the smooth muscle vasoconstriction and spasm [13]. Moreover, in a case of stiff-person syndrome, after the treatment of pregabalin, the rigidity and painful spasms dramatically improved and the patient could walk without assistance [22]. Consistent with a previous study, Poyraz M et al. found that five patients with cramps showed favorable response to pregabalin treatment [23]. Similarly, our study also showed an apparent therapeutic effect of pregabalin on mandible activity and the degree of trismus severity. There was also a case report of muscle rigidity associated with pregabalin [24] as well as pregabalin-induced trismus in a leukaemia patient [25]. Therefore, the mechanism involved in pregabalin for trismus may be related to the mechanism mentioned above. Few studies investigating the mechanism of pregabalin for trismus are present in the literature, and further studies focusing on the underlying molecular mechanism of pregabalin in radiotherapy-induced trismus are necessary both in vitro and in vivo. Additionally, as the limitation of this study is the small sample size, larger prospective studies will be required to clarify our findings.

More important, we found that the physical health and whole life domain of WHOQOL-BREF were significantly improved in trismus patients with pregabalin treatment. The maxed dose was 300mg/d, and the whole treatment time was 8 weeks. No serious adverse effects were found. Previous studies reported that the side effects for pregabalin included dizziness, somnolence, headache, blurred vision, edema and weight gain [26]. And severe side effects often presented in a dose-dependent manner. In our study, we observed dizziness (36.7%) and somnolence (23.3%) at the beginning of the treatment with pregabalin. But patients can tolerate these side effects by starting with low dose and increasing the dose gradually. Additionally, if the trismus is released, pregabalin can continue to be used combined with rehabilitation for several days and then gradually reduced. Because pregabalin is a symptomatic therapy for radiotherapy-induced trismus, mandibular rehabilitation is also important.

Although the results presented in this study are encouraging, there are still several limitations of the findings. First, this is a retrospective study in a single center. Second, sample size in this

study was small. Despite these limitations, the findings of this project are able to provide an early evidence for the effectiveness of pregabalin treatment in improving trismus and QOL in NPC patients with radiotherapy-induced trismus. Additionally, in our study, a number of *P* values was between 0.05 and 0.005, which was considered as "suggestive" results [27]. Thus, further research eliminating methodological bias and enhancing statistical power with larger samples will be required to clarify out findings.

5. Conclusion

In conclusion, our hospital-based, retrospective cohort study suggested that administration of pregabalin, in adjunct to rehabilitation, might provide a better outcome in NPC patients with radiotherapy-induced trismus. Pregabalin was an effective and safe drug for radiotherapy-induced trismus in NPC patients. Larger prospective studies will be required to validate the effect of pregabalin.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgement

This study was funded by National Natural Science Foundation of China (No. 81471249, 81622041), Major Program of Collaborative Innovation Specialized in Livehood Science Topics (201604020097), Science and Technology Planning Project of Guangdong Province (2016A050502016), and Tip-top Scientific and Technical Innovative Youth Talents of the Guangdong special support program (No. 2016TQ03R559) to Yamei Tang.

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