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Effects of rosiglitazone on quality of life and prognosis of patients with early stage glottic laryngeal carcinoma

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Abstract: Early-stage glottic laryngeal carcinoma refers to Tis-T2 lesions without cervical lymph nodes involvement and distant metastasis. Rosiglitazone facilitates expression of anti-inflammatory substances in the body, protecting immune system and improving patient's treatment efficacy and prognosis. We aimed to clarify the influence of rosiglitazone on prognosis of early-stage glottic laryngeal carcinoma. The control group received low-temperature plasma radiofrequency ablation, and the observation group additionally received rosiglitazone; 4 mg, 2 times/day for 6 months. After treatment, the observation group showed reduction in the fundamental frequency perturbation and amplitude perturbation and increase in the harmonic-to-noise ratio relative to the control group. Total effective rate was 80.31% and 77.14% for observation and control groups, respectively ($P > 0.05$). Peripheral blood immune makers were higher in the observation group. The incidence rates of adverse reactions were lower in the observation group. The median survival time was 33 months in control group and 47 months in observation group ($P < 0.05$). The five-year survival rate was 77.14% in the observation group and 54.29% in the control group ($P < 0.05$). Rosiglitazone can prolong the survival of early-stage glottic laryngeal carcinoma patients, improving immune function and reducing adverse reactions during treatment.

Keywords: Glottic laryngeal carcinoma (GLC), efficacy of rosiglitazone, quality of life, survival rate.

INTRODUCTION

Early-stage glottic laryngeal carcinoma (GLC) refers to Tis-T2 lesions without cervical lymph nodes and distant metastasis (Angel *et al*., 2011). Laryngeal carcinoma (LC) is a common malignancy in head and neck and takes up 5.7%-7.6% of systemic malignancies. The age of onset is 50-70 years old and it is more common in men than women. GLC is the most common type of LC, accounting for 50%-70% of LC (Kasper *et al*., 2011). With the continuous improvement of the diagnosis and treatment level of LC, the treatment of GLC is focused more on the protection of laryngeal function, the integrity of laryngeal structure, the preservation of laryngeal function, the reduction of recurrence rate, etc. (Bibby *et al.*, 2008). The current treatments for LC are surgery and radiotherapy. Nevertheless, surgery will destroy the normal structure of the larynx, seriously affect the patients' vocal function and there are many postoperative complications and so the postoperative quality of life will be low. These cause the non-surgical treatment to replace the surgical treatment as the main treatment modality in GLC (Higgins *et al*., 2009). Recently, with the development of photodynamic technology and the optimization of chemotherapy drugs, photodynamic technology has been gradually applied to therapy of GLC (Kujath *et al*., 2011). Though photodynamic technology has achieved certain clinical efficacy in treating GLC, its adverse reactions cannot be ignored, especially for elderly patients with weakened immunity. Thus, elevating immunity and reducing adverse reactions are crucial for elderly patients with locally advanced LC.

Rosiglitazone can facilitate the expression of anti-inflammatory substances such as adiponectin, etc., in the body, reduce the tissue damage caused by excessive inflammatory response, protect the patients' immune system and systemic tissues and ultimately elevate patients' treatment efficacy and improve final prognosis (Rasteniene *et al*., 2015). Nevertheless, there are few reports on clinical efficacy of rosiglitazone in treating early-stage GLC. Thus, this study attempted to clarify influence of rosiglitazone on quality of life and prognosis of early-stage GLC patients.

GLC makes up a large percentage of laryngeal carcinoma. Because early-stage GLC is more responsive to curative therapy, laryngeal function, recurrence rates and quality of life should be prioritized. The standard GLC surgery can harm vocal function and produce postoperative issues, lowering patient quality of life. As a result, non-surgical therapy methods have become popular, although they may have side effects, particularly among elderly individuals with impaired immune systems. Rosiglitazone guards immunity and systemic tissues, improving therapeutic efficacy and prognosis in other medical conditions. Early-stage GLC treatment research is not very common. This study examines how rosiglitazone impacts early-stage GLC patients' quality of life and prognosis. The study seeks to discover rosiglitazone's possible benefits in GLC treatment. Rosiglitazone's therapeutic efficacy in early-stage GLC is not established

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yet. This study examines the effects of rosiglitazone on immune function and quality of life to identify novel therapeutic approaches that may improve patient outcomes and treatment efficacy. The study evaluates immunological function, adverse responses, overall quality of life, short-term clinical efficacy, speech function and the likelihood of survival.

MATERIALS AND METHODS

General data

Seventy early-stage GLC patients enrolled from January 2015 to December 2020, were divided into observation group (n = 35) and control group (n = 35) in a random manner. There were 34 men and 1 woman in study group with the age ranging from 42 to 83 (62.1 ± 1.6) years. The disease duration was 1-4 (3.1 ± 0.7) months. There were 33 men and 2 women in control group; the age ranged 40-88 (62.2 ± 1.7) years; the disease duration was 1-4 (3.1 ± 0.7) months. General data presented no difference between two groups ($p>0.05$). This study was approved by the ethical committee of the college and all patients or their families were informed and signed informed consents. Inclusion criteria: All patients were diagnosed with GLC and met the relevant clinical staging criteria for the disease. Exclusion criteria: (1) Those with various malignancies; (2) those with contraindications to surgery; (3) those with liver and kidney dysfunction; (4) those with immune system diseases.

Treatment methods

The patients in control group received low-temperature plasma (LTPT) radiofrequency ablation (RFA): An ion radiofrequency instrument was used. Participants were told to lie flat on their backs and given tracheal intubation and intravenous compound anesthesia. The laryngoscope entered through the mouth, fully exposing the glottis and an endoscope was used to strictly check the scope, size, etc., of the lesions. The power of the equipment was adjusted; hemostasis was set to point 3 and the ablation to point 7. After the laryngoscope was used to lift the lesion, the cutter head was used to cut off the tumor and part of the vocal cords at a distance of 5 cm from the base. For patients with anterior commissure lesions, it was necessary to bend the front end of the cutter head to excise the lesions to the cartilage part. After operation, they were given warm and semi-liquid food for 1 week and intravenous infusion of antibiotics for anti-infection treatment and they were asked to be silent for 1 week and keep their voice for 1 month.

The observation group received rosiglitazone (4mg, per orally, 2 times/day) in addition to the therapy received by the control group. Treatment was continued for 6 months.

Both observational and control group received low-temperature plasma (LTPT) radiofrequency ablation (RFA). Control group additionally used rosiglitazone per-orally.

Evaluation indicators

1) The pronunciation function was analyzed by the German XION multi-functional acoustic analysis software and equipment, the ambient noise was less than 45 dB and the fundamental frequency perturbation, the amplitude perturbation and the harmonic-to-noise ratio of patients were measured.

2) Short-term clinical efficacy: The laryngeal CT, laryngoscopy, chest CT, etc., in two groups were reviewed 1 month after treatment. Assessment was conducted according to the Response Evaluation Criteria in Solid Tumors (RECIST) and divided into partial response (PR), complete response (CR), stable disease (SD) and progress disease (PD). The total response rate (RR) was CR plus PR.

3) Immune function: Flow cytometry detected T cells (CD3+, CD4+, CD8+, CD4+/CD8+ and NK cells) in peripheral blood of patients before treatment and 1 month after treatment.

4) Adverse reactions: The acute and subacute toxicity grading standards developed by the WHO respectively recorded the adverse reactions in two groups.

5) The quality of life was assessed using the Medical Outcomes Study (MOS) item short-from health survey (SF-36) (Rastenienė *et al*., 2015) developed by the Boston Health Research Institute, including Role-Physical (RP), Physical Functioning (PF), General Health (GH), Bodily Pain (BP), Social Functioning (SF), Role-Emotional (RE), Vitality (VT) and Mental Health (MH). Each dimension has 100 points and higher scores suggested better quality of life.

6) The 5-year survival status of patients in two groups was compared.

Ethical approval

This study involving human subjects was approved by the Yongchuan District People's Hospital in Chongqing, China (with reference to the letter number PH-A-16373). Written informed consent has been signed by each participant.

STATISTICAL ANALYSIS

Data was collected and analyzed using SPSS version 22. Paired t-test was taken for comparison between observation and control groups. $P < 0.05$ was considered to be statistically significant.

RESULTS

Comparison of pronunciation function

Before treatment, pronunciation function presented no difference between two groups ($p>0.05$). In comparison to the control group after treatment, the observation group

displayed decrease in amplitude perturbation and fundamental frequency perturbation and increase in harmonic-to-noise ratio ($p<0.05$, table 1).

Comparison of short-term clinical efficacy

One month after treatment, observation group has total effective rate of 80.31% and this index for control group is 77.14%. Total effective rate presented no difference between two groups ($x^2 = 0.102$, $p>0.05$, fig. 1).

Comparison of immune function

Following therapy for one month, there was a statistically significant increase in the number of CD3+, CD4+, CD4+/CD8+ and NK cells in two of the groups, but the number of CD8+ cells dropped (P 0.05). In addition, the levels of these immune makers found in the peripheral blood (CD3+, CD4+, CD4+/CD8+ and NK cells) showed an increase in the observation group in comparison to the control group, whereas the level of CD8+ showed a decrease (p 0.05, fig. 2).

Comparison of adverse reactions

The prevalence of unfavorable events such as swallowing dysfunction, infection, nausea and vomiting, liver and kidney damage and pharyngeal leakage were reduced in the observation group as compared to the control group (p 0.05, table 2). This was the case in both groups.

Comparison of quality of life

Before treatment, there was no significant change in the SF-36 scale scores of either group for any of the dimensions ($p>0.05$). After receiving treatment, the scores on each dimension increased in both groups. In addition, the scores of RP, PF, GH and MH were greater in the observation group as compared to the control group (p 0.01, table 3).

Survival analysis in two groups

Following therapy, both groups underwent five years of observation, during which time two patients in the observation group and three patients in the control group were lost to follow-up. In the observation group, the median survival time was 47 months (95% confidence interval: 40.78-50.25), which was considerably longer than the 33 months (95% confidence interval: 27.16-38.44) in the control group (X2 = 11.492, p 0.05). The survival rate at five years was 77.14% (27/35) in the observation group, which was substantially greater than the survival rate at five years of 54.29% (19/35) in the control group (X2 = 5.732, p 0.05, fig. 3).

DISCUSSION

Laryngeal cancer is a common malignant tumor disease in clinical practice and the incidence of the disease is related to factors such as viral infection, air pollution, alcoholism, sex hormone disorders, etc. The pathogenesis of the disease is complex and no unified conclusion has been made in clinical practice (Agrawal *et al*., 2008). According to research statistics, early-stage GLC accounts for about 60% of primary LC. The disease has no marked clinical manifestations. With the development of the disease course, the disease will gradually affect the daily life of patients (Eckel *et al*., 1993). The larynx is a special part and a vital organ of the human body. For the treatment of this disease, it is generally believed in clinical practice that when removing the lesion, it is necessary to reduce the damage to the patients' tissue function and ensure the patients' quality of life after surgery (Ambrosh *et al*., 2011).

PPAR-γ, the target molecule of rosiglitazone, is a kind of nuclear transcription factor activated by ligands, which can increase the function of T cells and enhance the killing power of NK cells by facilitating synthesis of colony-stimulating factors, stimulating the differentiation and regeneration of myeloid cells, thereby improving patients' immunity (Smith *et al*., 1989). Rosiglitazone used for advanced non-small cell lung cancer can remarkably increase CD3+, CD4+, CD4+/CD8+ and NK cell levels in peripheral blood of patients and reduce CD8+ cell levels (Sandoval *et al*., 2010). Xu *et al., 2011* also demonstrated that after administration of rosiglitazone capsules for chemotherapy patients with advanced gastric cancer, CD3+, CD4+, T-suppressor and NK cells of patients all presented elevation, while those of patients with chemotherapy alone presented decline. Patients taking rosiglitazone capsules also had less bone marrow suppression (Xu *et al*., 2011). The above results all revealed that rosiglitazone capsules can improve patients' immunity. Herein, after 1 month of treatment, CD3+, CD4+, CD4+/CD8+ and NK cell levels presented elevation and CD8+ level presented depletion in observation group compared with control group, suggesting that rosiglitazone can enhance the immunity of elderly patients with locally advanced LC.

Moreover, herein, the incidences of adverse reactions such as leukopenia, thrombocytopenia, nausea and vomiting, liver and kidney damage, throat response, etc., were higher in observation group than control group. A study also has demonstrated that in treating multiple myeloma patients, the incidence of leukopenia, thrombocytopenia, nausea and vomiting and other adverse reactions in patients treated with Trimethoprim (TMP) chemotherapy + rosiglitazone presented depletion relative to that with TMP chemotherapy alone. Additionally, in gastric cancer, colorectal cancer, non-small cell lung cancer, etc., the incidence of adverse reactions of radiochemotherapy patients additionally administrated with rosiglitazone presented depletion relative to that of radiochemotherapy alone (Marx *et al*., 2002). Herein, rosiglitazone has been demonstrated to reduce the adverse reactions caused by LC treatment and improve patients' quality of life.

Table 1: The pronunciation function in two groups before and after surgery

Groups	Fundamental frequency perturbation ($\times 10^9$/L)		Amplitude perturbation (%)		Harmonic-to-noise ratio (dB)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation(n = 35)	1.41 ± 0.12	1.14± 0.09	4.67 ± 0.44	4.02 ± 0.35	18.47 ± 1.65	21.92 ± 2.04
Control(n = 35)	1.44 ± 0.13	1.31 ± 0.11	4.65 ± 0.43	4.31 ± 0.40	18.51 ± 1.66	20.03 ± 1.85
t-test value	0.865	6.099	0.166	2.782	0.087	3.499
p-value	0.391	< 0.001*	0.869	0.008*	0.931	0.001*

*****p-value suggests that the treatment has significantly improved the results

Table 2: Adverse reactions in two groups

Groups	Infection n(%)	Swallowing dysfunction n(%)	Pharyngeal leakagen(%)	Nausea and vomitingn(%)	Liver and kidney damagen(%)	Adversereaction rate (%)
Observation(n = 35)	0 (0.00%)	1 (2.86%)	1 (2.86%)	2 (5.72%)	0 (0.00%)	11.44%
Control(n = 35)	1 (2.86%)	3 (8.58%)	2 (5.72%)	5 (14.30%)	1 (2.86%)	34.32%

Grading of Adverse Outcomes: Grade 1: Mild Symptomatic or non-symptomatic and need no intervention, Grade 2: Moderate, minimum intervention needed, Grade 3: Severe or clinically significant but not life threatening, Grade 4: Consequences with a high risk of death; immediate action is needed, Grade 5: Mortality associated with AE(30)

Table 3: Quality of life in two groups

*Dimension	Before or after treatment	Observation group(n = 35)	Control group (n = 35)	t	P
PF	Before	45.10 ± 6.22	44.43 ± 7.11	0.449	0.654
	After	76.19 ± 9.01[ab]	64.56 ± 8.10[a]	6.008	0.000
RP	Before	47.66 ± 8.15	48.21 ± 9.11	-0.285	0.777
	After	80.00 ± 8.91[ab]	71.03 ± 9.05[a]	4.448	0.000
BP	Before	25.30 ± 5.65	26.40 ± 7.12	-0.771	0.443
	After	77.09 ± 12.22[ab]	63.12 ± 11.0[a].	5.318	0.000
GH	Before	37.80 ± 6.11	38.3 ± 7.32	-0.340	0.735
	After	75.52 ± 9.42[ab]	69.71 ± l0.2[a]	2.643	0.010
VT	Before	65.34 ± 8.12	65.12 ± 9.13	0.114	0.910
	After	79.90 ± 11.21[a]	79.03 ± 9.08	0.376	0.708
SF	Before	61.09 ± 10.04	59.42 ± 10.41	0.728	0.469
	After	83.20 ± 9.22[a]	82.11 ± 9.70[a]	0.514	0.609
RE	Before	58.80 ± 9.11	58.10 ± 9.32	0.338	0.736
	After	72.20 ± 8.02[a]	71.07 ± 7.95[a]	0.629	0.531
MH	Before	64.43 ± 8.92	63.6 ± 9.30	0.401	0.689
	After	80.01 ± 7.88[ab]	73.67 ± 8.85[a]	3.387	0.001

Note: [a] $p<0.05$ versus before treatment; [b] $p<0.05$ versus control group. * Role-Physical (RP), Physical Functioning (PF), General Health (GH), Bodily Pain (BP), Social Functioning (SF), Role-Emotional (RE), Vitality (VT) and Mental Health (MH).

The effect of rosiglitazone is to suppress the function of surface aminopeptidase by binding to immune cells, thereby elevating cell immune function, increasing patients' immunity and reducing the adverse reactions of radiochemotherapy (Marx *et al*., 2002).

Additionally, herein, short-term efficacy showed no statistically significant difference between two groups, but the 5-year survival rate was higher in observation group than control group, suggesting that rosiglitazone may be beneficial to elevate the prognosis of patients with early-stage GLC. This may be related to the anti-tumor role of rosiglitazone, which can repress tumor proliferation and metastasis by interfering with tumor cell metabolism, suppressing tumor cell proliferation, facilitating tumor cell apoptosis, etc. (Wang *et al*., 2020). Additionally, rosiglitazone can also stimulate immune responses through immunomodulatory agents, thereby suppressing tumor cell growth and progression (Morley *et al*., 2017). Thiazolidinedione decrease urine albumin excretion and might stop the progression of renal damage. According to a previous study, rosiglitazone therapy prevents type 2 diabetic patients' kidneys from gradually deteriorating (Kim *et al*., 2009).

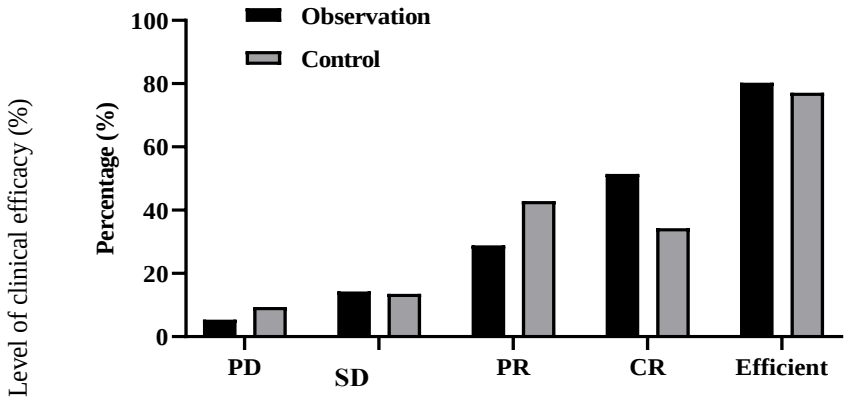

Fig. 1: Short-term clinical efficacy in two groups (Observation: n = 35, Control: n = 35)

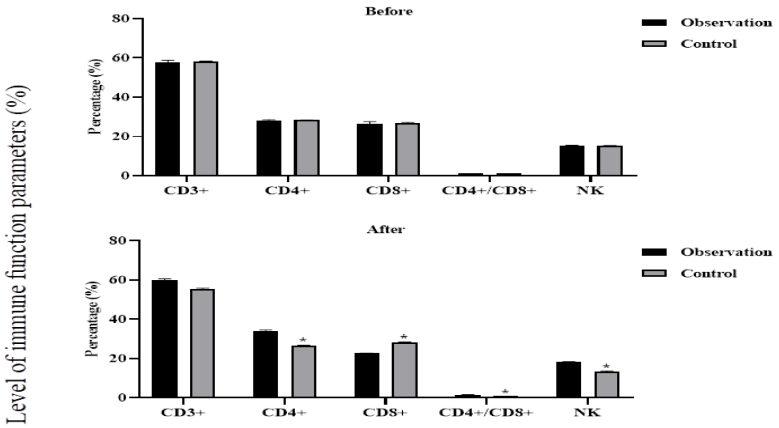

Fig. 2: Immune function in two groups before and after treatment
*p<0.05 versus control groups (Observation: n = 35, Control: n = 35)

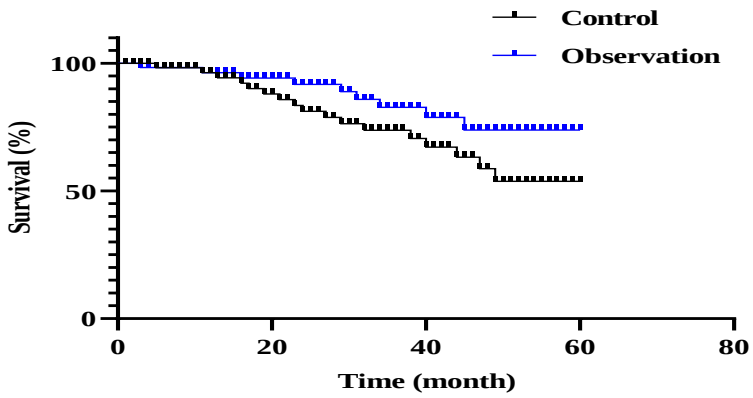

Fig. 3: 5-year survival rate in two groups (Observation: n = 35, Control: n = 35)

One study results showed that veterans with type 2 diabetes who took chlorpropamide, glipizide, glyburide, insulin and rosiglitazone had higher severity-adjusted death rates. The documented higher mortality could not be justified by the concomitant use of other, non-diabetic groups of drugs (Kheubek *et al*., 2013). While in the short term use, rosiglitazone is an insulin sensitizer that is both effective and safe when used as monotherapy in individuals with type 2 diabetes whose condition is insufficiently controlled by changes in lifestyle (Herold *et al*., 2001). Care must be taken when administering rosiglitazone because long term use may cause renal damage. It can also affect other vital organs. Rosiglitazone increases incidence of heart failure and other cardiovascular risks, according to the findings (Home *et al*., 2007).

Even while experimental evidence points to a preventive effect of peroxisome proliferator-activated receptor-gamma agonists against malignancies, the results of

available epidemiological research on the prevalence of cancer in people on rosiglitazone are not conclusive. Regarding the likelihood of developing cancer, rosiglitazone use seems to be risk-free (Monami *et al*., 2008).

Peroxisome proliferator-activated receptor (PPAR) is a nuclear steroid receptor that is activated by both natural substances like certain fatty acids and artificial substances like thiazolidinedione anti-diabetic medications. According to a previous study's findings, PPAR signaling is affected locally and systemically in early-stage breast cancer patients who receive short-term rosiglitazone medication (Lisa *et al*., 2007). In the present study, positive outcomes were also observed.

The small sample size (n=70) may limit generalizability and statistical power to find significant group differences. Even when patients were randomly assigned to observation and control groups, selection bias can occur. Subjectivity requires blinding. Cancer patients, especially early-stage ones, need lengthy follow-up to assess long-term survival and treatment side effects. The study being conducted at single medical center may limit patient population and treatments. Other treatments or interventions may have affected the outcomes. The study's patient age range, 40-88 years, may not adequately represent the elderly population.

CONCLUSION

In conclusion, rosiglitazone can improve the 5-year survival rate of early-stage GLC patients, elevate the immune function and quality of life and reduce adverse reactions during treatment, which is an ideal application when used in addition to low-temperature plasma (LTPT) radiofrequency ablation (RFA) and is worthy of clinical promotion. It is not meant to replace LTPT therapy, but when used additionally brings true outcomes in improving patient’s survival and prognosis

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