Bahrain Medical Bulletin, Vol.23, No.3, September 2001

To Evaluate the Effect of Wobe Mugos Hydrolytic Enzyme Therapy on Inflammation Induced by External Radiotherapy in Patients of Head and Neck Cancers

Objective: Our aim of this study was to evaluate the effect of enzymes in reducing inflammation produced by external radiotherapy.

Methods: Fifty consecutive patients of oral and oropharyngeal cancers under going external radiotherapy as the modality of treatment were alternated in two groups. A group of 25 patients were treated with external radiotherapy and 3 tablets of Wobe-enzyme three times a day. Other group of 25 patients were treated with conventional radiotherapy alone.

Results: In the control group of patients who received radiotherapy only, we found 8% of patients had grade I, 68% had grade II, 24% had grade III mucosal reaction respectively. In comparison to the enzyme group the mucosal reaction found that 76% had grade I, 14% had grade II and only 10% had grade III respectively. The data had significant P value. Nutritional status and Quality of life also improved in enzyme group.

Conclusion: In our study we found hydrolytic enzymes offers several advantages over routinely used anti inflammatory agents. They include better vascularisation of mucosa, improved microcirculation, elimination of undesirable products of inflammation. Wobe-enzyme is innovative, improved advancement designed to focus on acute and sub acute inflammation of various origins. They are prerequisite of good patient compliance and economical therapy.

Bahrain Med Bull 2001;23(3):116-18.

Enzyme system constitute an essential component of life for humans, animals and plants. They serve as the body labor force to perform all functions of our organ system. During the past 40 years, oral hydrolytic enzymes have been used in Europe and other countries as an approved, ethically and widely accepted modality of treatment for a variety of conditions. The European pharmacological and medical literature cites the mechanism of action of hydrolytic enzymes as an anti inflammatory, anti-oedema and fibrinolytic[1].

Modern development in field of radiotherapy has resulted in unbelievable bonanza of design and versatility of computerized treatment planning system and delivery systems machines. In spite of all developments, it is a known fact that external radiation, causes inevitable transient reactions due to inflammation of the part of body being radiated. This inflammation of mucosal membrane of oral cavity, oropharynx causes pain, difficulty in swallowing and speech thus resulting in poor compliance and poor quality of life[2].

In a country like India due to low socio demographic profile and inadequate medical facilities available, patients come in advanced stage of disease. So radiation is the main stay of treatment in commonly occurring cancer especially of head and neck region.

For the past several years, hydrolytic enzymes have been used in Europe and the United States as a potent anti inflammatory agent. The Indian subcontinent for the first time hydrolytic enzymes are being marketed as medicine made up of papain, bromelain, rutin, trypsin and chymotrypsin. We carried out a prospective randomized phase III clinical trial to evaluate effect of Wobe-mugos hydrolytic enzyme therapy on inflammation induced by external radiotherapy in patients of head and neck cancers. As we cater to a vast population suffering from head and neck cancers the main treatment modality offered to them is radiotherapy which is accompanied by transient but stressful inflammatory reactions. Our aim of this study was to evaluate the effect of enzymes in reducing inflammation produced by external radiotherapy so, that we could help our patients to over come this treatment related morbidity and help them to attain optimum quality of life.

METHODS

A prospective randomized phase three clinical trial was designed to evaluate the effect of Wobe Mugos hydrolytic enzyme therapy on the inflammation induced by external radiotherapy in head and neck cancer patients. Randomization of 50 patients of squamous cell carcinoma of head and neck cancer stages T_1-T_4, N_0-N_2, Mo fulfilling other inclusion criteria were allocated RT plus enzyme group in 25 patients and RT group in another 25 patients.

Inclusion Criteria

1. Proven biopsy
2. <65 years of age
3. No metastasis
4. No prior CT and RT

Prior to the start of radiation therapy and after the end of therapy anterior buccal excisional biopsy from the area radiated 5 mm x 5 mm x 5 mm was taken. The biopsy were blinded and subjected to evaluation by pathologist. 3 tablets of Wobenzyme were given three times a day with plenty of water. The therapy began 3 days prior to RT until 1 week after completion of radiation schedule. Radiotherapy was prescribed 60 Gy/30 fractions/ 6 weeks in both arms.

Evaluation was done clinically on weekly basis according to EORTC scale and all the pre-RT biopsies and post RT biopsies were studied by histopathologist. Statistical analysis were performed by Mann Whitney U Wilcoxan Rank Test.

RESULTS

In our study we found that of the 50 patients who were randomized either in RT plus enzyme and RT group alone, 69.4% of patients completed treatment schedule without gap, 10.2% completed with gap due to social reasons, 16.3% were hospitalized for intravenous fluid and 4.1% had severe agonising reaction.

Figure 1. Graph showing mucosal reaction in RT group patients had grade II reaction till visit 9 and grade III till visit 11.

Figure 2. Graph showing mucosal reaction in RT plus enzyme group. Patients had grade I reaction till visit 9.

Clinically in the control group mucosites was found to be grade I in 8%, grade II in 68% and grade III in 24% of patients respectively (Fig 1). As compared the mucosal inflammatory reaction in enzyme group was grade I in 76% of patients, grade II in 14%, grade III in 10% of patients respectively (Fig 2). All the data of the 6^{th} weekly visit was analyzed to Mann Whitney Wilcoxan rank sum test and the results were statistically significant (Table 1).

Table 1. **P values for W test shows significant difference**

Visit	Mucositis (p value)
1	0.1447
4	0.001
6	0.000
8	0.0001
10	0.0475

The histopathological reports of all pre RT biopsies revealed no submucosal edema, intact basement membrane, no ulceration, continuity of epidermis, patent capillaries, moderate collagenisation and hyalinization. The biopsies of the post RT group taking enzymes during the schedule revealed minimal submucosal edema, slight erosion of basement membrane, patent capillaries and moderate amount of collagen fibres. Continuity of epidermis was noted with thinning at places (Fig 3). In comparison, the biopsies of post RT group revealed frank ulceration, disruption of basement membrane, disintegration of epithelial cells, significant amount of submucosal edema and minimal

amount of collagen fibres (Fig 4). Stastistically significant P value was noted in post RT biopsies (Table 2).

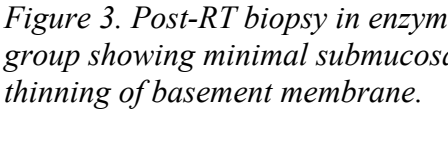

Figure 3. Post-RT biopsy in enzyme plus RT group showing minimal submucosal edema, thinning of basement membrane.

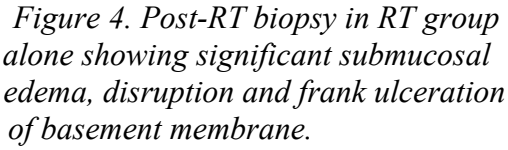

Figure 4. Post-RT biopsy in RT group alone showing significant submucosal edema, disruption and frank ulceration of basement membrane.

Table 2. **Wilcoxan Signed Rank Test of Biopsies (P values)**

	RT GROUP	ENZYME
Ulceration	0.034	0.180
Inflammation	0.044	0.206
Dysplasia	0.276	1.000
Spongiosis	0.218	0.059
Atrophy	0.564	0.059

Based on + and - ranks

Comment : P value is significant in RT group, ulceration and inflammation is markedly seen in post-RT biopsies. In enzyme group there is minimal change in such parameters.

DISCUSSION

MuGos GmbH & Co introduced wobe-enzyme hydrolytic oral enzymes 25 years ago. Since then it has been used worldwide with great success as a potent anti inflammatory, fibrinolytic and anti edematous drug.

Kameke[3] found that enzymes facilitate and accelerate the biological restoration of inflammatory processes. Enzymes improve, alleviate and clear up the effects of inflammation and to a large extent limit them. Similarly Maehder[4] found that the enzymes breaks antigen antibody which play role in pathogenesis of autoimmune disease. Dittmar[5] observed a good outcome after wobe-enzyme treatment in patients with pelvic

inflammatory disease. The enzyme group received 5 enzyme tablets tid and control group received a non steroidal anti inflammatory drug at usual dosage. Dittmar performed examination of WBC, ESR, bacteriological examination before start of therapy and then on 7^{th} and 14^{th} day. Wobe enzyme therapy led to an improvement in laboratory data and gynaecological findings on the 14^{th} day . The control group complaints took a longer time before recovery.

Rahn[6] extended the indication of Wobe-enzyme in vascular reconstructive surgery of lower extremities. He studied 80 patients in a double blind study. All patients had III to IV degree arterial occlusion. Three days prior to surgery, the study group and control groups began taking one tea spoon of granulated wobe- enzyme or an equal amount of placebo t.i.d respectively. The therapy continued for 14 days. Assessment of treatment was based on measurement of the circumference of leg, edema, pain score, local temperature, ESR, WBC, Quicks time and anti thrombin III. He found that the enzyme group had significantly better treatment outcome.

Presently wobe-enzyme is being widely used for HIV infections. The results of an initial pilot study carried out by Jager[7] on 40 patients in Walter Reed stages 1-5 revealed the excellent tolerance of enzyme therapy. There was an improvement in the general and nutritional status as well as the functional capacity of the patients. The severity of symptoms was reduced and the reactivity of the Merieun Multitest was clearly improved.

Data from our study support the effectiveness of wobe-enzyme in reducing sub mucosal edema, pain and lethality of rapidly progressive inflammation. Wobe-enzyme use avoid complication, shortens the duration of hospitalization thus improving the compliance and quality of life of our patients.

CONCLUSION

In our study we found Wobe-enzyme hydrolytic enzymes are potent anti inflammatory agents which can be safely practised in our clinical practice. Histological assessment confirmed the healing effect of enzymes in the form of collagenisation, increase in hyalinasation and spongiosis. It also possesses notable effect on elimination of undesirable products of inflammation which often leads to exacerbation of condition and its chronicity.

In conclusion these enzymes present a highly promising modality of medical treatment and represent the "medicines of the future". It's use is likely to increase as more clinical and scientific studies are conducted especially in utilizing it for various clinical conditions with emphasis on long term results.

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