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RESEARCH ARTICLES

Superoxidase dismutase (SOD) topical use in oncologic patients: treatment of acute cutaneous toxicity secondary to radiotherapy

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Abstract
Objective The objective of this study is to evaluate the efficiency of SOD applied topically in oncologic patients affected by acute radiodermatitis.
Materials and method This study includes 57 patients who showed a dermatitis grade 2 or superior; they were administered SOD ointment b.i.d. (40 mg, weekly) and follow-up continued for 12 weeks.
Results At the end of radiotherapy, 77.1% of the patients ameliorated completely or partially, and at the end of the 12-week period 100% of patients were free of toxicity. No acute toxicity relapses were reported. Response time reduced during radiotherapy, as well as the treatment time at the end of it.
Conclusions The employment of SOD topically is efficient in the treatment of radiodermatitis, which is an acute side effect of radiotherapy.

Keywords Superoxide dismutase · Radiodermatitis · Orgotein · Topical route

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Introduction

The employment of radiotherapy in the treatment of malign tumours has always implied the involvement of healthy tissue next to the tumour. The effect that ionising radiation has on the water molecules of tissues is well known [1]; it is produced by the hydrolysis of water molecules into superoxide radicals from oxygen (O_2, HO–), where they have the ability to trigger inflammatory processes on the tissues affected [2–4].

In a natural manner, the organism tries to counteract the effect of oxygen-free radicals by the action of different enzymes; endogenous superoxide dismutase is one of the most important enzymes [5]. The main problem of endogenous SOD is that it acts intracellularly [6, 7], so it cannot cross the cell membrane to eliminate free radicals from the extracellular liquid.

The utility of the SOD enzyme is widely demonstrated both for the treatment of inflammatory processes related to side effects of radiotherapy [8–13] and other processes triggered by oxygen-free radicals [14–17].

As the skin is the entrance of external radiations during the treatment of all tumours, radiodermatitis is regarded as one of the side effects that occurs more frequently and affects people both by the pain it produces and the aesthetic effect it has.

The objective of this study is to test the efficiency of SOD administered topically in the treatment of acute radiodermatitis, as well as its ability to prevent the interruption of radiotherapy treatments.

Material and methods

Patients

The study includes 57 patients with acute radiodermatitis grade 2 or superior, according to RTOG [18] and EORTC

Table 1 Summary of oncologic treatments

			CHMT-T			Total
			No	Previous	Concomitant	
Previous surgery	No	Count (% of total)	6 (10.5)	4 (7.0)	8 (14.0)	18 (31.6)
	Yes	Count (% of total)	22 (38.6)	10 (17.5)	7 (12.3)	39 (68.4)
Total	Count (% of total)	28 (49.1)	14 (24.6)	15 (26.3)	57 (100.0)	

[19] scales on acute toxicity, who underwent external radiotherapy (ERT) at the Servicio de Oncología Radioterápica del Hospital Central de la Defensa (Radiotherapy Oncology Department at the Central Military Hospital).

Of this group of 57 patients, 52.5% (30) were males and 47.4% were females; the average age was 60.33 years (range, 31–87).

Tumour localisation: 31 patients (54.4%) showed head and neck tumours, 27 patients (29.8%) breast cancer and 9 patients (15.8%) diverse tumour localisations (prostate, rectum or ovary tumours).

Oncologic treatments comprised surgery, previous chemotherapy or concomitant with ERT and all patients underwent ERT (Table 1).

ERT administered to patients is that specified in protocols for each case, where it varies between 50 and 66 Gy with conventional fractioning from 180 to 200 cGy per session, five sessions a week for 5–7 weeks.

SOD treatment

SOD administration is based on a galenic formulation in the form of an ointment, polyethylene glycol (PEG 4000), which is added to a superoxide dismutase solution (4 mg/ml) that is obtained from a commercial formulation of orgotein and benzylic alcohol 2% that acts as a preservative agent. The total amount of preparation administered weekly is 40 mg in two daily applications. SOD treatment begins when cutaneous toxicity reaches grade 2 or superior, and it ends when normality is restored (grade 0), or at the end of the 12-week period after treatment started. Maximum time of treatment is established at 12 weeks according to EORTC rules for acute toxicity periods.

Evaluation criteria

The adequate evaluation of effect evolution is established by a revision calendar: V0 represents basal visit (when toxicity was diagnosed); V1, first week after treatment; V2, two weeks later; V3, three weeks later; V4, 8 weeks later; and V5, 12 weeks after SOD treatment started. The treatment comprised non-parametric statistical tests to determine significant differences of toxicity in each visit and differences among frequencies and mean values χ^2 was determined by Friedman's ANOVA, which was used to compare proportions; other trials included nonparametric tests for determining Wilcoxon sign-rank on 2-way data, and Mann–Whitney test for independent samples.

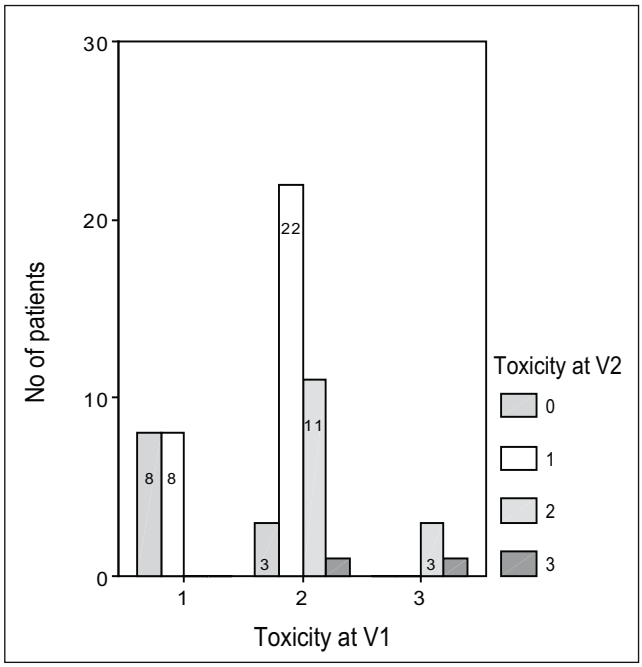

Fig. 1 Evolution of toxicity at V_1 and V_2

Results

Fifty-seven patients were assessed in the first visit (V0): 43 (75.4%) showed toxicity grade 2 and 14 patients (24.6%) showed toxicity grade 3.

At V1, one week after SOD treatment, 16 patients (28.1%) showed toxicity grade 1, 37 patients (64.9%) showed grade 2 and 4 patients (7%) showed grade 3.

At V2, two weeks after treatment, 11 patients (19.3%) showed total remission of acute toxicity (grade 0), grade 1 was observed in 30 patients (52.6%) grade 2 in 14 patients (24.6%), and 2 patients (3.5%) still showed grade 3 (Fig. 1).

At revision V3, four weeks had elapsed under SOD treatment, that is to say, 2 weeks from the previous revision; therefore patients who showed toxicity grade 0 in V2 were out of pharmacological treatment during this period. We report 37 patients (64.9%) showing grade 0, 15 patients (26.3%) showing grade 1, 4 patients (7%) showing grade 2 and 1 patient (1.8%) showing grade 3 (Fig. 2).

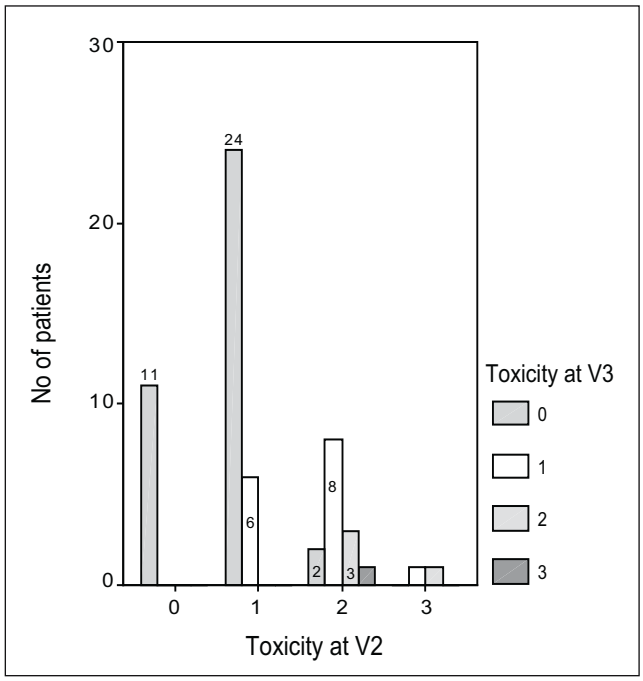

Fig. 2 Evolution of toxicity at V_2 and V_3

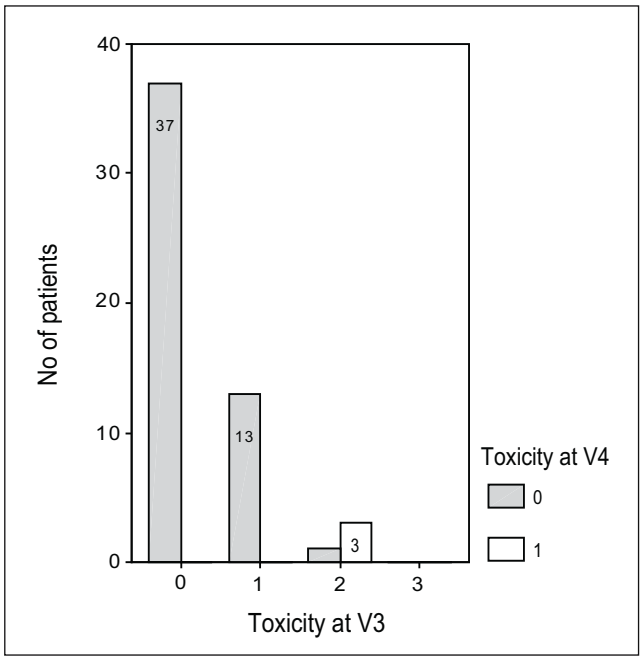

Fig. 3 Evolution of toxicity between the 4th and 8th weeks

At V4, eight weeks of follow-up had already elapsed. Three patients did not attend their visits and could not be accounted for, while 54 patients were still under assessment. From this group, 51 patients (89.5%) showed toxicity grade 0 and the remaining 3 patients (5.3%) showed grade 1 (Fig. 3). Evolution of toxicity grades from the time treatment began is shown in Table 2.

At the final visit (V5), 2 more patients did not attend the visits established by the calendar. At this last revision, at the end of a period of 12 weeks, we observed that no signs of acute toxicity were observed in the group of 52 assessable patients, so their grade was 0.

Al in all, a 77.1% value was obtained at the end of radiotherapy (17.5% for total response and 59.6% for partial response); no worsening of the condition was observed at the end of the 12-week period –this would represent the period of acute toxicity– so toxicity remission was complete.

As for radiodermatitis and its evolution during treatment, no significant differences were found with regard to sex, age, tumour localisation and existence or otherwise of other oncologic treatments.

In our study, our patients received radiotherapy treatment for an average time of 7.45 weeks. In this period, patients received topical treatment with SOD for 7.45 weeks. The time needed for continuing the treatment against toxicity at the end of radiotherapy was 2.1 weeks. Figures regarding evolution of patients from toxicity diagnosis to end of radiotherapy are listed in Table 3.

We must bear in mind that the average time for toxicity signs to remit was 2.22 weeks (Fig. 4), so amelioration began when the patients were still under radiotherapy treatment. The average time for total remission of toxicity was 4.58 weeks. Figures on the evolution of toxicity from the beginning of treatment to the end of the 12-week period are listed in Fig. 5.

Table 2 Evolution of toxicity since the start of SOD treatment

Visits	RTOG				Total
	0	1	2	3	
V_0			43 (75.4%)	14 (24.6%)	57
V_1		16 (28.1%)	37 (64.9%)	4 (7%)	57
V_2	11 (19.3%)	30 (52.6%)	14 (26.4%)	2 (3.5%)	57
V_3	37 (64.9%)	15 (26.3%)	4 (7%)	1 (1.8%)	57
V_4	51 (89.5%)	3 (5.3%)			54a
V_5	52 (91.2%)				52a

[a]Three patients did not attend visits at V_4 and V_5

Table 3 Evolution of patients from V_0 to end of ERT

			RTOG end of RT				Total
			0	1	2	3	
Initial RTOG	2	Count (% of total)	7 (12.3)	25 (43.9)	11 (19.3)		43 (75.4)
	3	Count (% of total)	3 (5.3)	5 (8.8)	4 (7.0)	2 (3.5)	14 (24.6)
Total	Count (% of total)	10 (17.5)	30 (52.6)	15 (26.3)	2 (3.5)	57 (100.0)	

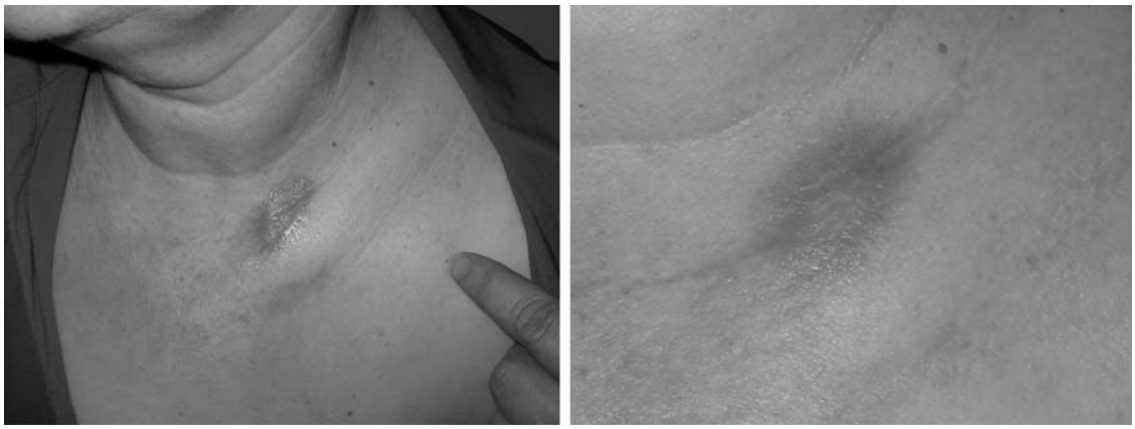

Fig. 4 Evolution of a patient in the RTOG 2 in the first week of treatment

Discussion

The use of radiotherapy for the treatment of tumours is more and more successful in the healing of this condition. Limitations of the treatment are mainly determined by the side effects that ionising radiations produce.

Although radiodermatitis is not the main side effect of radiotherapy, it is the most frequent. It leads to tissue damage and triggers pain. Pain may force patients to give up treatment, with the result that they alter the treatment planning and recovery. Some authors [20] think that hygienic measures may be employed and toxicity under grade 3 may be endured without medication during the radiotherapy period. For cases with a higher grade, they suggest discontinuation of the treatment and treatment of toxicity with corticoids.

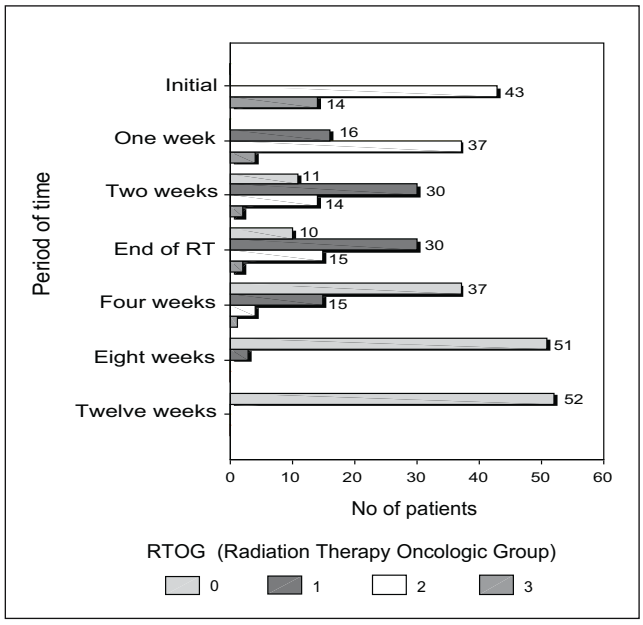

Fig. 5 Evolution of toxicity at each visit

The results we obtained demonstrate that toxicity may be controlled while patients undergo radiotherapy treatments. Hygienic measures make toxicity remission possible in 4–6 weeks once radiotherapy has ended. The data we have obtained proves that this period of time may be reduced to 2.1 weeks as soon as radiotherapy has ended.

Bibliographic revisions indicate there are no studies on acute radiodermatitis treated topically with SOD. Some prevention studies [21] on patients treated systemically reveal there are no differences between the group treated with SOD and the group treated without it.

Topical application has always been the method used on chronic toxicities [22–24], in cases where lesions are late and treatment periods are long –6 months– and results in amelioration vary between 40% and 92%; this includes those patients who meliorated and those who healed completely.

The results we have obtained are very similar to those from the centre of Valencia and collaborators [25, 26], where the use of SOD systemically for the treatment of acute toxicity yielded a value of 92% among patients who meliorated partially and those who meliorated completely.

Conclusions

We can conclude, after the analysis of the results, that this pharmacologic topical route developed for administering SOD is effective. This topical treatment has proved it can control radiotherapy toxicity while it is being administered; it shows a 77.1% of response at the end of radiotherapy (17.5% of total response and 59.6% of partial response). No worsening of the condition is observed at the end of the 12-week period –the period of acute toxicity– and the remission of toxicity is total.

Topical SOD reduces the time of toxicity remission during radiotherapy; it also reduces the time that toxicity takes to disappear after treatment. No relapses of acute toxicity are produced.

Topical SOD does not require hospitalisation, not even outpatient treatment in a healthcare centre, as patients may administer it themselves at home. This improves the quality of life of oncologic patients. Besides, this topical route is not an aggressive one.

Therefore, we can conclude that the topical administration of SOD is an effective alternative for the treatment of radiodermatitis.

References

1. Nakano T, Oka K, Taniguchi N (1996) Manganese superoxide dismutase expression correlates with p53 status and local recurrence of cervical carcinoma treated with radiation therapy. Cancer Res 56:2771–2775
2. Buell MG, Hording RK (1989) Proinflammatory effects of local abdominal irradiation on rat GI tract. Dig Dis Sci 34:390–399
3. De AK, Rajan RR, Krishnamoorthy L et al (1995) Oxidative stress in radiation-induced interstitial pneumonitis in the rat. Int J Radiat Biol 68:405–409
4. Epperly M, Bray J, Kraeger S et al (1998) Prevention of late effects of irradiation lung damage by manganese superoxide dismutase gene therapy. Gen Ther 5:196–208
5. McCord JM, Fridovich I (1969) Superoxide dismutase: an enzymatic function for erythrocuprein (hemocuprein). J Biol Chem 244:6049–6055
6. Esco R, Valencia J, Bascon N et al (2003) Prevención de toxicidad rectal tardía radioinducida. Estudio randomizado. Rev Oncología 5:190
7. Esco R, Valencia J, Bascon N et al (2003) Estudio randomizado de prevención de toxicidad radioinducida tardía pélvica mediante Ontosein®. Rev Oncología 5:190
8. Valencia J, Polo S, Velilla C et al (2001) Impacto del uso de orgoteina en la prevención de esofagitis por irradiación en el carcinoma microcítico pulmonar. Rev Oncología 3:204
9. Valencia J, Polo S, Bascon N et al (2000) Orgoteina asociada a radioterapia en cancer de cabeza y cuello. Control de la toxicidad. Rev Oncología 2:137
10. Edsmyr F, Menander Huber KB (1981) Orgotein efficacy in ameliorating side effects due to radiation therapy. Eur J Rheum Inflamm 4:228–236
11. Edsmyr F, Huber W, Menander KB (1976) Orgotein efficacy in ameliorating side effects due to radiation therapy. Double-blind, placebo-controlled trial in patients with bladder tumors. Curr Ther Res 19:198–211
12. Maberger H, Hubert W, Menandert Hubert KB, Bartsch G (1981) Orgotein: a new drug for the treatment of radiation cystitis. Eur J Rheum Inflamm 4:244–249
13. Menander Huber KB, Edsmyr F, Huber W (1980) Orgotein efficacy in ameliorating side effects due to radiation therapy. Scand J Urol Nephrol 55:219–224
14. Vaca JM, Vegas M, Merino R (1997) Epidural orgotein in failed back syndrome. II Congress of the European Federation of IAPS 1997. Barcelona, Spain
15. Ruiz A, Gil R (1999) Tratamiento del dolor mediante administración intradérmica de una solución compuesta por anestésico local+antiinflamatorio+analgésico. IV congreso de la SED, Málaga, Spain
16. Reig E (1994) Sistemas de infusión de fármacos en el tratamiento del dolor. Rev Soc Esp Dolor 1:14–20
17. Rodríguez-López M, Camba A, Contreras D, Torres LM (2003) Multicenter clinical trial of epidural orgotein versus placebo in patients with chronic intractable spinal pain. Pain Clin 15:7–15
18. Rubin P, Constine LS, Fajardo LF et al (1995) Overview: late effects of normal tissues (LENT) scoring system. Int J Radiat Oncol Biol Phys 3: 1041–1042
19. Cox JD, Stetz JA, Pajak TF (1995) Toxicity criteria of radiation therapy oncology group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 31:1341–1346
20. Fuentes R, Canals E, Vayreda J (2003) Tratamientos de soporte en oncología radioterápica. Servicio de Oncología Radioterápica. Institut Catalá d'Oncolgia, Girona (9):40–43
21. Sanchiz F, Millá A (1996) Prevention with orgotein of radioinduced secondary effects in patients with head and neck tumours. VIII Biennial Meeting International Society for Free Radical Research, Paris, France
22. Perderau B, Campana F, Vilcoq JR et al (1994) Superoxyde dismutase (Cu/Zn) en application cutanée dans le traitment des fibrose radioinduites. Bull Cancer 81:659–669
23. Benyahia B, Campana F, Perderau B et al (1996) Effects of superoxide dismutase topical treatment on human skin radiofibrosis: a pathological study. Breast 5:75–81
24. Campana F, Zervoudis S, Perdereau B et al (2004) Topical superoxide dismutase reduces post-irradiation breast cancer fibrosis. J Cel Mol Med 8:109–116
25. Valencia J, Bascon N, Polo S et al (2000) Orgotein impact on radiotherapy acute side effects in head and neck cancer. Radiother Oncol 56:411
26. Valencia J, Velilla C, Urpegui A et al (2002) The efficacy of orgotein in the treatment of acute toxicity due to radiotherapy on head and neck tumors. Tumori 88:385–389