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Clinical Study of Hydrogen Peroxide Infusion for Paranasal Carcinoma

(paranasal carcinoma/peroxide infusion/oxygen tension)

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The oxygen and carbon dioxide tensions in the normal and tumor areas with 0.12% hydrogen peroxide infusion were measured continuously with a medical mass spectrometer at the beginning of infusion and after several infusions, in 17 patients with paranasal carcinoma.

There was no significant difference in the oxygen tension in tissue between the normal area and tumor area at the beginning of infusion.

The oxygen tension rose slowly after the start of infusion, reached a peak at around the end of infusion and fell off rapidly (rapid down type) after completion of infusion, in many patients, both in the normal and tumor areas at the beginning of infusion, while the slow down type or slow up type was observed in many cases after several infusions.

The oxygen tension and the margin of rise after several infusions were low compared with findings the beginning of infusion, both in the normal and tumor areas.

The carbon dioxide tension of infusion showed no marked variation.

When the preoperative effect was studied by Shimozato's classification, only 28.6% of the cases were judged to be cases of Grade III. The 5-year survival rate was 50 percent.

We have conducted a study of the combined therapy of 0.12% hydrogen peroxide infusion and external irradiation of ^{60}Co for the purpose of raising the oxygen tension and increasing the sensitivity of radiation in the tumor region in hopes of enhancing the therapeutic results of paranasal carcinomas (1).

We carried out continuous measurements of changes in the oxygen tension in the tumor region, with hydrogen peroxide infusion, using a medical mass spectrometer.

Effectiveness of preoperative treatments hitherto conducted was studied histopathologically to obtain reference material.

MATERIALS AND METHODS

The 17 subjects studied were patients with paranasal carcinoma who had been admitted to Department of Oto-rhino-laryngology, Tottori University

School of Medicine in and after June, 1976.

Sixteen were classified as cases of maxillary cancer and one as ethmoidal cancer.

Histopathologically, all were squamous cell carcinoma, expect for one with carcinoma simplex (Table I).

TABLE I. *Materials*

Case	Age	Sex	Chief complaint	TNM	Note
1	54	m.	r. nasal bleeding	T3 N0 M0	
2	62	m.	r. cheek swelling	T3 N0 M0	
3	54	m.	r. nasal obstruction	T3 N0 M0	
4	62	f.	r. cheek swelling	T3 N0 M0	
5	68	f.	r. cheek swelling	T3 N1 M0	
6	52	m.	r. cheek swelling	T3 N0 M0	
7	52	f.	r. cheek swelling	T3 N0 M0	
8	67	m.	r. cheek swelling	T3 N0 M0	
9	57	f.	r. nasal obstruction	T3 N0 M0	
10	64	m.	r. cheek swelling	T3 N0 M0	
11	71	m.	l. nasal obstruction	T3 N0 M0	
12	62	m.	l. nasal obstruction	T3 N0 M0	
13	69	f.	r. nasal bleeding	T2 N0 M0	ethmoidal sinus
14	64	m.	l. cheek swelling	T3 N0 M0	
15	51	m.	l. cheek swelling	T3 N0 M0	
16	70	f.	r. cheek swelling	T4 N3 M0	
17	54	m.	r. cheek swelling	T4 N0 M0	

When a clinical diagnosis was made, ^{60}Co external irradiation in doses of about 1000 R (200 R per day) was prescribed. After that, an observation window was made in the maxillary sinus to confirm the histological findings after which external carotid intubation was carried out.

5-Fluorouracil 250mg dissolved in 5% dextrose solution was injected by the one-shot method and then 5% dextrose-Ringer's solution 250ml containing Oxydol 10ml and Nicotinic acid 40mg was infused over a one hour period.

Immediately after completion of the infusion, ^{60}Co external irradiation was applied.

The procedure described above was conducted daily for about 10 days, bringing the total dose of irradiation to 3000 R.

A medical mass spectrometer (MEDSPECT, MS 8) was used to measure the tissue oxygen tension and carbon dioxide tension on 0.12% hydrogen peroxide infusion.

A teflon catheter for measurement of tissue gas was introduced into the normal soft tissue of the buccal area and tumor tissue anterior or lateral to the maxillary sinus, and continuous measurement was made mainly of changes in the local oxygen tension at the beginning of hydrogen peroxide infusion (1−2 infusions, average 1400 R irradiated) and after several infusions (6−7 infusions, average 2200 R irradiated).

RESULTS

Oxygen Tension in the Normal Tissue

The oxygen tension in the normal tissue at the beginning of infusion is shown in Table II. The tension in the buccal area was distributed between 24 and 45 mmHg, averaging 38 mmHg.

TABLE II. *Oxygen Tension in Normal and Tumor Tissues*

Normal	38 ± 4 (5)
Tumor	37 ± 10 (12)

Values are the mean ± standard deviation.
Number of cases are shown in parenthesis.

Oxygen Tension in the Tumor Tissue

The oxygen tension in the tumor tissue at the beginning of infusion is shown in Table II. The tension was distributed over a considerably wide range of 17 to 53 mmHg, averaging 37 mmHg.

Variation Curve for Oxygen Tension in the Normal Tissue

The tension rose slowly after initiation of hydrogen peroxide infusion in all cases and tended to reach a peak at around the end of infusion.

The mode of variations of the oxygen tension immediately after completion of the infusion could be classified into three types, namely, the rapid down type, slow down type and slow up type (Fig. 1).

a. The rapid down type : Where the oxygen tension, immediately after completion of the infusion, falls off at the rate of 15 mmHg or more during 10 min.
b. The slow down type : Where the oxygen tension falls off at the rate of not more than 15 mmHg during 10 min.
c. The slow up type : Where the oxygen tension does not tend to fall off but shows a tendency to rise slightly.

In Table III shows changes in the oxygen tension in the buccal area on hydrogen peroxide infusion.

In 4 out of 5 there was a rapid down type at the beginning of infusion, while the rapid down type decreased in number, only 1 of 5, and the slow down type or slow up type was observed in many patients, after several infusions. The oxygen tension before the start of infusion averaged 38 ± 4 mmHg at the beginning of infusion and 20 ± 3 mmHg after several infusions : that is, the oxygen tension after several infusions dropped by 47% over that at the beginning of infusion, the changes being statistically significant ($P < 0.05$).

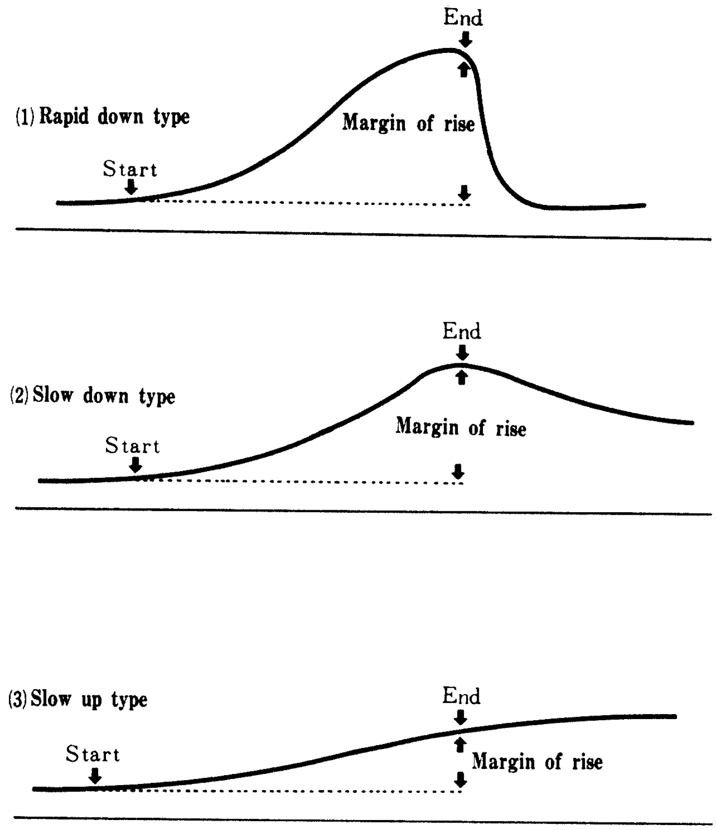

Fig. 1. Variation curve of oxygen tension.

TABLE III. *Variation Curve of Oxygen Tension in Normal Tissue*

Case	Beginning of infusion			Several infusions		
	Before infusion (mmHg)	Variation curve	Margin of rise (mmHg)	Before infusion (mmHg)	Variation curve	Margin of rise (mmHg)
1	38	rapid down	74	20	slow down	58
3	44	rapid down	20	18	slow down	6
11	45	rapid down	37	15	rapid down	57
12	24	slow down	18	24	slow up	13
13	39	rapid down	40	21	slow down	32
M	38		38	20		33
SD	4		22	3		24

Assuming that the difference between the oxygen tension before the start of infusion and that on completion is the margin of rise in the oxygen tension, the oxygen tension showed a rise in all cases at the beginning of infusion and the margin of rise averaged 38 ± 22 mmHg or a 100% increase over that before the start of infusion, the changes being statistically significant ($P < 0.02$).

The oxygen tension showed a rise in all patients, even after several infusions and the margin of rise averaged 33 ± 24 mmHg or a 165% increase over that before the start of infusion, the changes being statistically significant

($P < 0.05$). The margin of rise in the oxygen tension after several infusions decreased in 4 of 5 cases compared with the margin of rise at the beginning of infusion, but there was no statistically significant difference.

Variation Curve for Oxygen Tension in the Tumor Tissue

Changes in the oxygen tension in the tumor tissue were measured at the beginning of infusion and after several infusions, results of which are summarized in Table IV.

TABLE IV. *Variation Curve for Oxygen Tension in Tumor Tissue*

Case	Beginning of infusion			Several infusions		
	Before infusion (mmHg)	Variation curve	Margin of rise (mmHg)	Before infusion (mmHg)	Variation curve	Margin of rise (mmHg)
2	35	rapid down	124	28	slow down	13
4	36	rapid down	104	18	slow down	44
5	45	rapid down	30	11	slow up	7
6	43	rapid down	40	38	slow down	7
7	53	slow down	15	60	slow down	19
8	32	slow down	12	13	slow up	35
9	41	slow down	10	37	slow up	8
10	17	rapid down	17	15	slow down	14
14	36	rapid down	38	25	slow down	19
15	27	slow down	21	53	slow down	13
16	31	rapid down	66	47	rapid down	32
M	36		43	31		19
SD	10		39	17		12

The variation curve at the beginning of infusion showed many cases of the rapid down type (7 of 11 cases) as in the normal tissue, while the rapid down type decreased in number (1 of 11 cases) and the slow down type or slow up type was observed in many cases after several infusions.

The oxygen tension before the start of infusion averaged 36 ± 10 mmHg at the beginning of infusion and 31 ± 17 mmHg after several infusions. The oxygen tension fell off by 14% after several infusions over that at the beginning of infusion, but the changes were not statistically significant.

The variation curve for the oxygen tension in the tumor tissue showed a pattern quite similar to that in the normal tissue.

A rise in the oxygen tension was observed in all patients at the beginning of infusion.

The margin of rise in the oxygen tension averaged 43 ± 39 mmHg, a 119% increase over that before the start of infusion, changes being statistically significant ($P < 0.01$).

The rise in the oxygen tension was noted in all patients even after several infusions.

The margin of rise in the oxygen tension averaged 19 ± 12 mmHg, a 61%

increase over that before the start of infusion, these changes being statistically significant ($P < 0.01$).

The margin of rise in the oxygen tension after several infusions decreased in 9 of 11 cases compared with that at the beginning of infusion, but there was no statistically significant difference.

In cases showing the rapid down type at tbe beginning of infusion, the time required for the oxygen tension to reach the level before the start of infusion from a sharp drop at the completion of infusion was designated as the oxygen tension decreasing time and the value decreased of the oxygen tension in the first 10 min after completion of the infusion was taken as the margin of decrease in the oxygen tension. These data together with the margin of rise are shown in Table V.

TABLE V. *Decreasing Pattern of Oxygen Tension in Tumor Tissue at Beginning of Infusion*

Case	Margin of rise (mmHg)	Margin of decrease (mmHg/10minutes)	Decrease rate (%)	Decreasing time (minutes)
2	124	115	93	18
4	104	100	96	15
5	30	19	63	18
6	40	22	55	21
10	17	18	106	16
14	38	22	58	17
16	66	72	109	19
M	60	53	83	18

In these cases, the margin of rise in the oxygen tension showed a fall of average 83% (decrease rate) in 10 min after completion of the infusion and the value for the oxygen tension before the start of infusion was restored in about 18 min.

Variation Curve for Carbon Dioxide Tension in the Normal and Tumor Tissues

The carbon dioxide tension was stable throughout the study in almost all cases with only a slight change of 10 mmHg observed. These cases were designated as the stabilizing type. In some patients, the oxygen tension rose and the carbon dioxide tension fell off after the start of infusion. Those showing such a pattern was designated as the descent type.

Table VI shows the mode of variations in the carbon dioxide tension in all patients.

Histopathological Study

To evaluate the preoperative effectiveness of the therapy based on the protocol mentioned earlier, we prepared serial sections of isolated preparations and studied the histopathology.

TABLE VI. *Variation Curve of Carbon Dioxide Tension*

Case	Beginning of infusion	Several infusions
1	stable	stable
2	〃	〃
3	〃	〃
4	〃	〃
5	〃	descent
6	〃	stable
7	〃	〃
8	〃	descent
9	〃	stable
10	〃	〃
11	〃	descent
12	descent	stable
13	stable	〃
14	〃	〃
15	〃	〃
16	〃	〃

The subjects included 56 with paranasal carcinoma who had been treated from December, 1972 to June, 1979. Fifty-one had squamous cell carcinoma. The effectiveness of the preoperative treatment on the tumor tissue was evaluated in accordance with Shimozato's classification (2).

The results were broken down to Grade IIA 15 cases, Grade IIB 25 cases, Grade III 13 cases and Grade IV 3 cases.

With cases of Grade III and Grade IV, there were only 16 cases (28.6%). When the relationship between local recurrence and Shimozato's classification was examined, 19 had a local recurrence among the 40 who were classified as Grade IIA or IIB. The site of recurrence in these cases was almost consistent with the site showing histologic findings of Grade IIA or IIB ; that is, the consistency was found in 17 of 19 cases (89%).

Therapeutic Results

The survival rate as of the end of April, 1980 is as follows. The survival of five years or more was observed in 9 of 18 cases (50%), followed by 4 years in 18 of 32 cases (56%), 3 years in 24 of 42 cases (57%), 2 years in 32 of 52 cases (62%) and 1 year in 44 of 56 cases (78%)

DISCUSSION

Oxygen Tension in the Tumor Tissue

The oxygen tension in the tumor tissue is known to be low compared with the normal tissue, as reported by Gray (3) and Churchill-Davidson *et al.* (4). In the present study, the oxygen tension averaged 38 ± 4 mmHg in the normal tissue and 37±10 mmHg in the tumor tissue, there being no statistically significant difference.

Umegaki and Egawa (5) reported that the oxygen tension in many areas of the tumor tissue is lower than that in the normal tissue but that the oxygen tension in an area around the tumor where proliferation is active is almost equal to or sometimes higher than in the normal tissue.

In the present study, the site of catheterization of the tumor tissue extended through the anterior wall of the maxillary sinus to the buccal area, and this is an area which corresponds to a peripheral area of the tumor and in which proliferation is relatively active.

This is probably why the oxygen tension in the tumor tissue showed a relatively high value.

Deschner and Gray (6) maintained that an increase in the sensitivity of radiation is rarely observed when the oxygen tension is 10 mmHg or more.

If that is the case, the oxygen effect can hardly be expected. In the present study, however, the value measured is considered as a mean of values measured in the local tissue at various distances from the vascular system, and it is surmised that hypoxic cells of 10 mmHg or less might exist at an area distant from the blood vessels in this local tissue.

The oxygen tension in the tumor after several infusions of hydrogen peroxide solution averaged 31±17 mmHg or a 14% decrease over that at the beginning of infusion and here there was no statistically significant difference. This is a problem related to the site of catheterization. Efforts were made to introduce the catheter into the same area.

Where the area of previous catheterization has become necrotic and sloughed off, catheterization should be made in an area near the peripheral region or near the normal region. A definite decrease in the oxygen tension was observed in 8 of 11 cases.

Thus, various factors are combined to decrease the local blood flow often which the oxygen tension in the tumor decreases.

Variations in the Oxygen Tension at the Beginning of Infusion

As to variations in the oxygen tension in the normal and tumor tissue on hydrogen peroxide infusion, Mallams *et al.* (7) reported that when 250ml of 0.12% solution was infused into rabbit muscle and the oxygen tension was measured quantitatively by the micro-electrode polarographic method, the oxygen tension rose gradually during the infusion and dropped sharply, simultaneously with completion of the infusion. Kamijo (8) infused 0.24% solution into the normal area and tumor area of the rat and measured changes in the oxygen tension by the platinum electrode polarographic method. He reported that the oxygen tension rose rapidly in the normal tissue but somewhat more slowly in the tumor and fell off relatively fast in both normal tissue and tumor. However, the process was slower in the tumor after completion of the infusion and variations in the oxygen tension were not so large as expected.

In the present study, the variation curve for the normal tissue showed that the oxygen tension rose slowly with the start of infusion, reached a peak at around the end of infusion, dropped sharply simultaneously with completion of the infusion and approached the pre-infusion level in a short time in 4 of 5 cases.

On the other hand, the pattern of the oxygen tension in the tumor tissue at the beginning of infusion was similar to that in the normal tissue in 7 of 11 cases, and there was no time lag in the ascent pattern of the oxygen tension between the normal and tumor tissue.

The margin of rise in the oxygen tension averaged 38±22 mmHg in the normal tissue and 43±39 mmHg in the tumor tissue, an increase of 100% and 119%, respectively, over the values obtained before the start of infusion, there being no finding, as reported by Sakamoto (9), Hokura (10) and Kamijo *et al.* that the margin of rise in the oxygen tension in the tumor is small. This is probably because the site of catheterization was a peripheral area of the tumor which abounds in the blood vessels and shows a relatively good blood flow, in other words, the circulatory condition in the tumor is similar to that in the normal tissue.

As to the timing of hydrogen peroxide infusion and irradiation, Mallams *et al.* reported (on the basis of results of an experiment with the infusion into rabbit muscle) that the last period of infusion is appropriate for irradiation.

In the present study also, in most of the patients there was a rapid down type at the beginning of infusion or when the tumor was relatively newly formed, and the oxygen tension reached a peak at around the end of infusion.

As shown in Table VI, the oxygen tension fell of at a rapid rate of 18–115 mmHg in the first 10 min from immediately after completion of the infusion, an 83% (mean) decrease in the margin of rise in the oxygen tension was apparent. The oxygen tension before the start of infusion was restored on an average of 18 min.

With the method we used by which irradiation was applied immediately after completion of the infusion, it is possible that irradiation was applied at a time when the oxygen tension fell off considerably.

Taking into consideration five min for irradiation and the time loss before irradiation, it would be more appropriate to place the patients in the irradiation room not more than 10 min before completion of the infusion and to apply irradiation while giving the infusion.

Variations in the Oxygen Tension after Several Infusions

According to the variation curve for the oxygen tension in the normal and tumor area after several infusions, the slow down type was observed in many cases and the margin of rise in the oxygen tension fell off in 4 of 5 in the normal area and 9 of 11 cases in the tumor area.

There is a tendency for changes in the oxygen tension after completion of the infusion to slow down and for the margin of rise in the oxygen tension to decrease both in the normal and tumor area after several infusions.

This indicates that the blood vessels are decreased because of cicatrization in the buccal area, due to surgical procedures in the case of normal area, and regression of the tumor due to combined therapy in the case of tumor area, and that the vascular distribution is decreased because of fiber formation in tissue around the tumor due to preoperative irradiation and a subsequent decrease in blood flow.

As described above, the blood flow in the tumor area decreased after several infusions ; clinically marked regression of the tumor was observed in this period and the margin of rise in the oxygen tension also showed a considerable fall compared with that at the beginning of infusion ; therefore, 5−7 hydrogen peroxide infusions would be appropriate and not much could be expected, if the frequency of infusion is further increased.

Variation in the Carbon Dioxide Tension

The variation curve for carbon dioxide tension showed a stabilizing type in most cases, demonstrating that no disturbance of local circulation occurred after hydrogen peroxide infusion.

If disturbance of circulation is caused by bubble formation and the blood flow decreases, the supply of oxygen to the local area and the oxygen tension in tissue will decrease and the carbon dioxide tension in the tissue will increased.

Histopathological Studies on the Preoperative Effect

The preoperative effect was studied by Shimozato's classification in those placed on a therapy of our own design.

As a result, a histologic effect of Grade III or above was found in only 16 (28.6%) of 56 cases.

Because of the short clinical period, no definite conclusion can be drawn. But the 5-year survival as of the present is 9 (50%) out of 18 cases, which is a slight improvement over the previous therapeutic results.

If the irradiation chance and infusion technique are improved further, better therapeutic results can be expected.

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