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COMPARATIVE CHARACTERISTICS OF DIFFERENT THERAPEUTIC EFFECTS ON SCAR PROCESSES IN THE LARYNX

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ABOUT ARTICLE

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Abstract: The most characteristic etiological factors of damage to the larynx and trachea are currently considered to be intubation, trauma and autoimmune diseases. These types of damage lead to an inflammatory process, which in the larynx and trachea has a tendency to a primary chronic course, affects the cartilaginous framework, is accompanied by persistent infiltration and tissue edema. Without targeted treatment, such an inflammatory process leads to the development of chondroperichondritis , followed by atresia of the larynx and cervical trachea above the tracheotomy tube, cicatricial narrowing of the thoracic trachea, persistent impairment of the vocal apparatus, and other consequences.

INTRODUCTION

One of the main manipulations used in intensive care units is the intubation of the larynx and trachea. For many decades, the only way to ensure free breathing in case of airway obstruction was tracheostomy. However, the last decades are characterized by the widespread use of endotracheal intubation [4,16-20]. The latter began to be used not only for anesthesia and effective care for acute airway obstruction, but also in cases of resuscitation requiring prolonged artificial lung ventilation (ALV) [1-3].

Often performed in extreme situations to restore adequate breathing, intubation itself is a rather traumatic manipulation for the laryngeal mucosa. At the same time, quite often, despite the observance of all the rules for intubation in patients with acute airway narrowing, it is necessary to resort to forced

insertion, which contributes to the application of excessive efforts to insert the tube into the lumen of the larynx in order to quickly achieve normal breathing and create adequate oxygenation [6]. As a result, the cricoarytenoid joint is often injured, vocal folds, subvocal region of the larynx and trachea [5].

Injury to the mucous membrane and elements of the larynx and trachea during the introduction of an endotracheal tube is confirmed by many works that reflect the results of pathomorphological studies of the larynx and trachea of patients undergoing prolonged intubation [7-12]. At the same time, in most cases, multiple injuries of the larynx and trachea were detected [13-17].

Results and their discussions. Based on the data of a morphological study of cicatricial strictures ¬of the larynx, we came to the conclusion that in order to reduce further proliferation of connective tissue in the lumen of the larynx, it is necessary to use drugs that would inhibit inflammation and infiltration and synthesis of the main substance of the connective tissue (collagen) at an early stage, reduce vascular permeability. For this, various factors affecting scar tissue are currently being used, which can significantly reduce scar formation and, accordingly, shorten the treatment time for patients with chronic cicatricial stenosis of the larynx and trachea. The main effect of these drugs is associated with the ability to influence the proliferative function of the connective tissue in order to suppress it.

Based on the foregoing, we conducted an experimental study to study the response of the tissue of the larynx and trachea in response to the use of factors that affect the processes of scarring.

For this, 40 homogeneous Chinchilla rabbits were selected (average weight 2.0 kg). The cicatricial process in the larynx was modeled by exposing and opening the anterior cervical trachea and creating a wound in the subvocal larynx using a conventional galvanocautery. In 20 animals a wound was created at the level of the posterior wall, in 20 others a circular wound was created. All animals were left with a tracheostomy.

Of the 40 rabbits, 11 died, mainly due to acute respiratory obstruction and mostly in the group with circular injury. The remaining animals were divided into groups: 1 and 2 - control, 3 - exposure to the hormonal drug triamcinolone acetonide (TA), 4 - exposure to the cytostatic antibiotic mitomycin C (MMC), and 5 - radiation therapy (RT).

All animals underwent cytomorphological, morphometric and immunohistochemical studies.

After a 4-week observation, 8 animals were sacrificed and their tissues were sent for histopathological examination. All the subjects had stenosis of the larynx, and the degree of stenosis varied from 20% to

50% in the group with isolated stenosis, and from 40% to 80% or more in the group with circular stenosis.

Histopathological examination of tissue samples showed the presence of ulceration of the mucous membrane of the larynx, the formation of granulation tissue, chondromalacia of damaged cartilage of the larynx, thickening of the submucosal layer with the formation of rough scarring.

The expression of the proliferating cell nuclear antigen (PCNA) and the apoptotic cell death marker p53 was also studied . This study is informative in the process of wound healing and regeneration of damaged tissues associated with the proliferation and apoptosis of cellular elements leading to the formation of scars of varying degrees. The results of studies in this direction showed that the proliferation of cellular elements was average, the mitotic index was equal to 1.9% o - 1.75%, the apoptotic index was low 2.75% and 2.25%, however, cell death was carried out mainly by the type of necrosis.

The results we obtained, presented in Table 1, also indicated an increase in the expression of p 53, which correlated well with the data of cytomorphological studies.

Later, in order to determine the effect of various agents on the process of scarring, some rabbits (21 animals) of groups 1 and 2 in the non-purulent phase of productive inflammation were administered TA, MMS, and RT was performed.

Table 1

Comparative indicators of factors affecting scar tissue

Group / Impact	MI, ‰	AI, %	PCNA H-points %	p 53 H-scores %
Control, n =8				
1 - isolated stenosis, (n = 4)	1.9±0.43	2.75±0.51	270±14.0	175±8.6
2 - circular stenosis, (n =4)	1.75±0.41	2.25±0.46	280±21.3	160±7.8
3rd - TA, n = 7	0.5±0.22 x	4.9±0.68 x	145±10.5 x	100±23.4 x
4th - MMS, n=7	0.7±0.26 x	5.9±0.74 x	130±18.2 x	60±19.6 x
5th - LT, n = 7; SOD 8	0.2±0.14 x	6.1±0.75 x	120±24.3 x	59±28.2 x

Note: x - comparison with control (p <0.05)

After 4 weeks of observation, all rabbits were measured the lumen of the larynx and tissue was taken for histological examination.

All experimental rabbits had stenosis of the larynx, however, the degree of stenosis depended on the method of influencing the scar tissue. Animals that received TA into the scar area showed a marked decrease in the degree of stenosis compared to the control groups.

Table 2

The degree of stenosis of the lumen of the larynx after the application of various factors affecting the scar tissue

GROUP OF ANIMALS	Degree of stenosis %	
	Circular stenosis	Isolated stenosis
	control	
	40% to 80%	20% to 50%
	experienced	
- receiving TA	40 % to 60%	10% to 30%
- receiving MMS	20% to 40%	10%
- receiving RT	30% - 40%	10%

In the group with isolated variants, the degree of stenosis varied from 10% to 30%. In the group with circular stenosis, it was higher and ranged from 40 % to 60% , respectively (Table 2).

The cytomorphological characteristics of the scarring process, independent of surgical intervention, were of the same type.

When comparing the morphological picture of the connective tissue of the larynx of rabbits that did not receive local corticosteroid therapy and animals that were injected with TA into the inflammation focus, it was clear ¬that this drug strongly inhibits the lymphoid inflammatory response and connective tissue proliferation.

After hormone therapy, it was found that the bundles of collagen fibers located around the blood vessels poorly perceived acidic dyes, while the fibroblasts in them were in a mature stage, differing in a fusiform shape and rod-shaped nuclei.

In other words, the connective tissue after exposure ¬to the hormone was in a state of atrophy. The study of cell death and proliferation indicators in this group of animals revealed that against the background of TA treatment, the MI indicator decreases by 3-4 times, and AI, on the contrary, increases by 1.8-2.0 times, respectively, compared with the untreated group of animals (Table 1).

PCNA protein , and apoptosis - p 53 (Table 1) showed a complete correlation with the morphological picture of the studied tissue.

Animals treated with MMC application showed a significant involution of scar connective tissue, which was expressed by a decrease in the degree of stenosis , especially in the group with isolated stenoses.

Compared with the control group, the degree of stenosis decreased to 10%. In the group with circular stenosis, the degree of stenosis also decreased from 20 % to 40%, respectively (Table 2). The results obtained in the group with circular stenosis, in our opinion, were associated with a greater involvement of the cricoid cartilage and the first tracheal rings in the process.

In the morphological analysis of samples taken from animals after the application of MMS, the removed pathological tissue was represented by a multilayer polymorphic epithelium, directly under which the connective tissue was manifested by diffuse and lymphohistiocytic infiltration with a single content of plasma cells. The fibers were thin, irregularly oriented. The lumens of some blood vessels are wide, the walls are thinned. In deeper layers, the density of infiltration was higher, but its focality was noted. Differently oriented thin collagen fibers were detected between cell clusters. There were also areas represented by a coarser fibrous tissue, between the fibers of which were located spindle-shaped-elongated fibroblasts with rod-shaped nuclei.

The study of AI and MI values in animals of this group, as well as in animals treated with TA, indicated a decrease in mitotic activity and an increase in apoptosis of scar tissue cells, which was also confirmed by the data obtained in the study of PCNA and p 53 proteins (Table 1).

In the group of animals, against the background of the results of the use of LT, inhibition of scarring was also observed, which was characterized by a decrease in its size due to local tissue atrophy. At the same

time, the axial size of the narrowed area of the larynx increased , and the degree of stenosis decreased to 10% in the isolated group and, accordingly, to 30% - 40% in the group of circular stenosis (Table 2).

The histological analysis of the tissues indicated a significant involution of the scar tissue , which was represented by bundles of oriented collagen fibers, which were loosened in places . Lymphoid infiltrates were rare. The cell groups consisted of macrophages, single plasma cells, and mature fibroblasts located in the environment of blood capillaries. Attention was drawn to some thickening of the walls of blood vessels and restoration of the structure of the epithelium over the scar. There was almost no proliferation of cellular elements, the mitotic index was 0.2 % o , but apoptosis induction was observed. The apoptotic index was 6.1%. The results obtained by us showed a slight difference between cytomorphological and immunohistochemical parameters, and their severity was statistically unreliable (Table 1).

A study using these therapeutic effects on scar tissue revealed their significant effectiveness on excessive scarring . When comparing the scar tissue of animals in the control and experimental groups, a different degree of stenosis of the respiratory tract was revealed, which was visually detected when measuring their lumen (Fig. 1,2)

This fact was confirmed by the results of morphometric and immunohistochemical studies.

Thus, the mitotic index, indicating the proliferative activity of the tissue in the animals of the studied groups , was significantly lower than in the control group. It should be noted that this was clearly manifested in the group with the use of radiation exposure, where the mitotic index was lower on average by 8-10 times. A slightly smaller difference was observed in the groups after the use of TA and MMS.

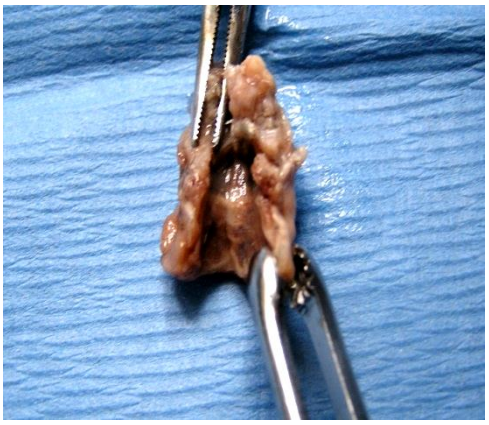

Fig. 1. Cicatricially modified area of the larynx of the animal of the studied control group

Rice. 2. Cicatricially modified part of the larynx of an animal of the group

Along with the mitotic index, certain changes were observed in the apoptotic index, which was also more pronounced in the group after the use of RT and MMS.

When comparing the applied factors of influence on the scar tissue of the larynx of animals among themselves, the most pronounced effect was observed when exposed to the beam and MMS. However, the effect of the beam as a whole on a living organism somewhat limits its use in a hospital, while the application effect of MMS on young scar tissue can be considered a fairly safe non-invasive manipulation.

CONCLUSIONS

Thus, the conducted studies made it possible to conclude on the expediency of the therapy we chose, which caused a significant decrease in proliferation and induction of apoptosis. This statement was confirmed by the results of cytomorphological, morphometric and immunohistochemical studies. At the same time, during the experiment, it was proved that it is necessary to simultaneously use immunohistochemical methods with the fullest possible set of markers of various cellular elements and tissue structures.

The information obtained will be the most objective when using various methods of morphometric analysis, which allow determining the exact localization, as well as the quantitative ratio of cellular elements and tissue structures in the damaged area.

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