

**LARYNGEAL GRANULOMA – BENEFIT IN TREATMENT
WITH ZINC SUPPLEMENTATION?**

LARINKSNI GRANULOM – KORIST OD TERAPIJE PREPARATIMA CINKA

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Summary: Laryngeal granulomas present as contact and postintubation ulcers and granulomas. Essentially, a contact granuloma is a pseudotumor of the lateral wall of the posterior glottis. The most common etiological factor is voice abuse, with predisposing factors such as reflux disease. Postintubation ulcers and granulomas, although of different etiology, according to all the other traits belong to this clinical entity. The therapy of choice is conservative treatment. Surgical laser excision is indicated for resistant cases and those whose size is causing respiratory distress. Treatment of laryngeal granulomas with zinc supplementation is reported in the literature as one of the forms of conservative treatment, and we wanted to consider it in this review. Zinc is an essential mineral that plays a vital role in many biochemical reactions and is considered very important for wound healing.

Keywords: conservative treatment, laryngeal granuloma, zinc supplementation

Kratak sadržaj: Larinksni granulom se predstavlja kontaktnim i postintubacionim ulkusom i granulomom. U suštini, kontaktni granulom je pseudotumorski izražaj lateralnog zida zadnjeg dela glotisa. Najčešći etiološki faktor je neodgovarajuća upotreba glasa, uz predisponirajuće faktore kao što je refluksna bolest. Postintubacioni ulkus i granulom, iako drugačije etiologije, po svim ostalim osobinama pripadaju ovom kliničkom entitetu. Preporučena terapija je konzervativno lečenje, a hirurška laserska ekscizija indikovana je za rezistentne slučajeve i one koji svojom veličinom izazivaju respiratorne smetnje. U literaturi se pominje peroralna primena preparata cinka u terapiji larinskog granuloma kao jedan od vidova konzervativnog lečenja, što smo i mi u ovom kratkom pregledu želeli da razmotrimo. Cink je esencijalni mineral koji igra ključnu ulogu u mnogim biohemij-skim reakcijama i smatra se da je veoma važan za zarastanje rana.

Ključne reči: konzervativna terapija, larinksni granulom, preparati cinka

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Laryngeal granuloma

Laryngeal granulomas present as contact and postintubation ulcers and granulomas. These benign inflammatory lesions are associated with injury to the posterior glottis (1). They are usually located over the vocal process of the arytenoid cartilage with corresponding ulcers on the contralateral side (2). Contact ulcers and contact granulomas are just different stages of the same pathological process. In the literature, they are described as arytenoid granuloma, vocal process granuloma, peptic granuloma, pyogenic granuloma, inflammatory polyp, granulomatous diseases of the larynx (Figure 1). This rare entity was first described as a contact ulcer of the larynx by Jackson in 1928. The first case of a postintubation laryngeal granuloma was reported by Clausen in 1932. While contact granulomas occur more frequently in men, postintubation granulomas are more often found in women. Children never develop contact granulomas, but it is possible to find postintubation granulomas. Contact granuloma rarely occurs in vocal professionals.

The etiology is still unclear. Essentially, a granuloma presents an inflammatory reaction in the perichondrium of the arytenoid cartilage, in response to mechanical or functional trauma; sometimes, it can be idiopathic. Mechanical trauma is caused by iatrogenic factors—prolonged intubation, inadequate size of the intubation tube, microlaryngeal surgery, laser surgery of the larynx, bronchoscopy. Phonotraumatic vocal behavior includes voice abuse, overuse and misuse of the voice, forced phonation especially in patients with a characteristic psychological profile and professions with authoritative vocal expressions. Risk factors affecting the formation of granulomas are severe cough, vomiting, gastroesophageal reflux disease, habitual throat cleaning, use of tobacco and alcohol, emotional stress (4, 5). The underlying pathogenesis involves inflammatory response, sec-

ondary healing, reparation as a result of perichondritis, epithelial hyperplasia and possible secondary infection. The basic pathological process is the loss of mucoperichondrium of the vocal process of the arytenoid (6). Subepithelial hemorrhage could cause persistence of a laryngeal granuloma. Histologically, a black spot can be found, as a sign of hemosiderin accumulation in the subepithelial layer, followed by infiltration of macrophages and lymphocytes (7) (Figure 2).

Clinical signs and symptoms include hoarseness, foreign body sensation, constant need of throat cleaning, sore and aching throat, dyspnea, trace of blood in sputum, but it could also be asymptomatic (2). Diagnosis is based on history, clinical examination, endovideolaryngostroboscopy, psychoacoustic analysis of the voice, multidimensional computer voice analysis, voice handicap index, reflux symptom index and reflux finding score.

Biopsy is only necessary for differentiation from a malignant lesion (2). In the differential diagnosis, one should be thinking of non-specific and specific inflammatory diseases, recurrent respiratory papillomatosis, malignant tumors (3).

The primary treatment is conservative therapy—intensive phoniatric rehabilitation (vocal and speech therapy, voice rest), inhalation (corticosteroids, pantothenol solution, saline), H₂ blockers or proton pump inhibitors. Surgical excision should be avoided because contact granulomas tend to recur. Laser or microlaryngoscopic surgery is only helpful in cases of large granulomas which compromise respiration (3). The literature describes an abundance of therapy regimens with augmentation for glottic occlusion, botulinum type A injection and injection of depot corticosteroid directly into the lesion, and low dose radiotherapy (8, 9). Incomplete removal of a granuloma does not have to mean lack of healing. Complete

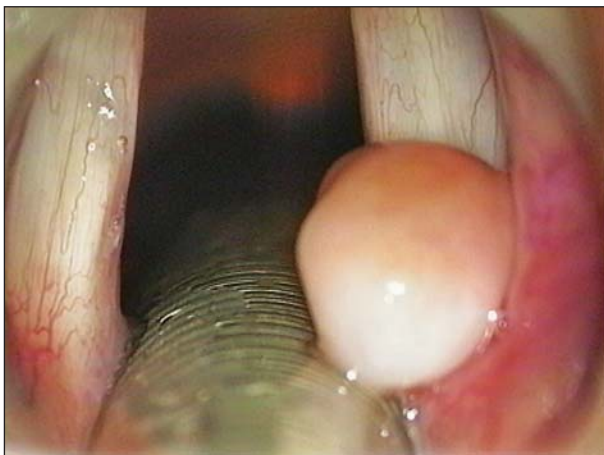


Figure 1 Endoscopic findings: typical appearance of a post-intubation granuloma of the vocal cord.

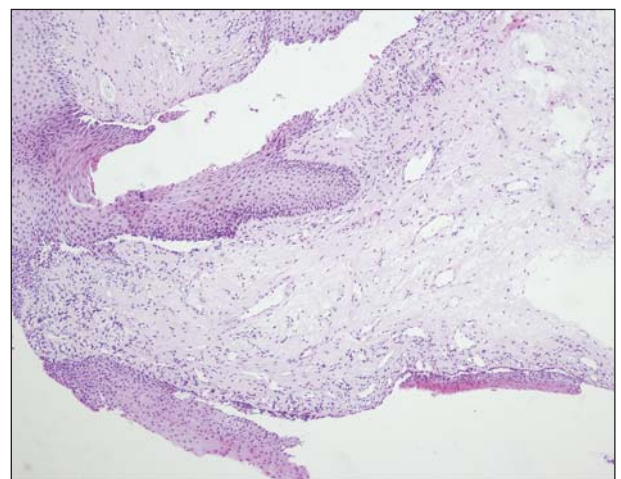


Figure 2 Histopathological findings of laryngeal granuloma.

removal of a granuloma is not necessarily a cure. The most important is prevention. Granulomas may disappear with conservative treatment with proton-pump inhibitors, vocal and speech therapy, inhalation with corticosteroids, or even spontaneously (1).

Zinc supplementation

Zinc is a potent catalyst of wound healing and zinc deficiency may be a common cause of delayed tissue repair. The use of zinc to promote healing is not new and it dates from the ancient Egyptians (10). Zinc is an essential mineral that plays a vital role in many biochemical reactions. Zinc is necessary for the functioning of more than 300 different enzymes, and is an important cofactor for antioxidant enzymes, so it is needed by the human body. Zinc possesses antiviral activity (11). Zinc is a major trace element in the wound healing process because of its involvement in many different cellular processes (12). It is found in the human body and averages 2–3 g in: erythrocytes and leukocytes, muscle, bone, skin and other organs. Zinc has a relatively short half-life of only 13.9 h and the treatment should last long enough, but over-dosage should be avoided. Zinc is necessary for normal fetal development, sensory perception (taste, smell, vision), controls the release of stored vitamin A from the liver, regulates insulin activity, promotes the conversion of the thyroid hormone thyroxine to triiodothyronine. Zinc may be effective in the treatment of many disorders, based on available scientific evidence: gastric ulcers, leg ulcers, skin conditions (eczema, psoriasis, acne vulgaris), gingivitis, immune disorders, infertility, Wilson's disease, herpes, taste or smell disorders, diabetes, diarrhea in malnourished children, sickle cell anemia, attention-deficit hyperactivity disorder. Very popular is the use of zinc in the prevention of common cold. Zinc gluconate appears to have beneficial effects on immune cells. Zinc oxide cream could be used to decrease excess granulation tissue reaction in open wound care and to decrease skin inflammation around tracheostoma (13, 14). Zinc can be measured in plasma, red blood cells, white blood cells and hair. Zinc deficiency in the human body is caused by inadequate intake, absorption or excretion. Symptoms of deficiency may be delayed wound healing, delayed sexual maturation, growth retardation, mental lethargy, weight loss, hair loss, taste changes. In preliminary clinical research, patients with head and neck cancers who received radiotherapy and were taking zinc supplementation had a better clinical outcome.

The current Mayo Clinic recommended dietary allowance for oral zinc supplementation is: 11 mg for males aged 19 years and older and pregnant females, 12 mg for lactating females, 8 mg for females aged 19 years and older, 2 mg for children aged 0–6 months, 3 mg for 7-month-olds to 3 years, 5 mg for 4–8-year-olds, 8 mg for 9–13-year-olds, 11 mg for

14–18-year-olds. For surgical incision wounds: 220 mg of zinc sulfate a day taken orally following surgery to promote wound healing.

Zinc supplementation is relatively safe and well tolerated when taken in recommended doses. Side effects have been reported as nausea, vomiting, diarrhea, unpleasant taste, anemia, intestinal bleeding, liver failure. Zinc may increase the risk of bleeding, lower blood sugar levels, reduce levels of HDL cholesterol. Zinc is involved in hemostasis and is necessary for antibody production and immune cell function (15). Zinc plays a central role in the proliferation of inflammatory cells and modulates cutaneous inflammation (16). Zinc inhibits bacterial growth (17). Generally, it is considered that zinc does influence the wound healing process, but the exact mechanisms for this are unclear (18–20). The evidence for routine zinc supplementation is poor. Some evidence suggests oral zinc supplementation in patients with zinc deficiency (12).

Zinc sulfate treatment for laryngeal granuloma

The literature provides some reports on the use of zinc sulfate in the treatment of laryngeal granuloma. Pullen (21) reported the efficacy of oral zinc sulfate in patients with postintubation granulations and stenosis of the glottis and subglottic area. Trial of oral zinc sulfate therapy was instituted by Marshak, in 1973, in five adults and one child, and it was useful in the treatment of postintubation granulomas (three adults and one child) as well as in contact ulcer granulomas (two adults). The adults were taking zinc sulfate tablets, 220 mg, three times a day and the child was placed on oral 50 mg zinc sulfate and after three weeks to three months the symptoms disappeared without recurrence during the following year. The recommendation was that treatment should extend three to four weeks after the resolution of granulomas (6). They commented that zinc sulfate therapy is advantageous in patients with laryngeal granulomas because of its simplicity, ability to preserve the anatomical and functional integrity of the vocal cords, the achievement of quick symptomatic relief, the avoidance of surgical excision and lack of toxic effects when using the recommended dosage. There is the possibility of using prophylactic zinc therapy in all the cases where prolonged intubation is expected.

Sun et al. (1) in the year 2012 reviewed the effects of zinc sulfate therapy in 16 patients (14 males and 2 females) with vocal process granulomas on the arytenoid cartilage, treated between 2005 and 2010 in an outpatient clinic. Eleven patients had a history of trauma or laryngeal intubation and 5 patients had unknown origin. The mean ages of granuloma occurrence were 47.7 in men and 30.5 in women. Every patient had one or more symptoms: hoarseness, sore

throat, lump sensation in the throat, cough in a period from 1 month to 2 years. They adopted an endoscopic grading system to classify the patients: grade I – sessile, non-ulcerative granuloma limited to the vocal process (3 cases); grade II – pedunculated or ulcerated granuloma limited to the vocal process (9 cases); grade III – granuloma extending past the vocal process but not crossing the midline of the airway in the fully abducted position (4 cases) and grade IV – granuloma extending past the vocal process and past the midline of the airway in the fully abducted position (no cases) (22). The granulomas were graded A if unilateral (13 cases) and B if bilateral (3 cases). Laryngeal granulomas may recur locally, particularly if the original inciting cause persists, but their maximum dimension rarely exceeds 3 cm because of their growth limitation (2, 22).

The patients were taking 100 mL of oral solution containing 200 mg zinc sulfate three times a day after meals. The vocal process granulomas were resolved in all the patients within 4–12 weeks and the symptoms improved. The granulomas did not recur in 15 of their patients after a one-year follow-up and in 1 patient for 5 years. They concluded that zinc sulfate therapy is good because it is a simple, safe and effective approach for resolving vocal process granulomas, either as an initial or compensatory treatment, especially in the cases of recurrence after failed surgeries (1).

The role of zinc is controversial in some cases and there are different opinions in the published studies. Yilmaz (23) believes that if zinc is expected to cure vocal process granulomas, the patients must be

deficient in zinc, so the levels of zinc should be measured in blood or tissue before treatment. Yilmaz made several comments on the manuscript of Sun et al. (1) because he did not expect their patients to be deficient in zinc, and put forward the question: how can zinc sulfate be the perfect cure for vocal process granuloma, without any recurrence even 1 year after treatment.

Conclusions

Evidently, zinc is a necessary oligoelement in many functions of the human body, especially in the wound healing process of injuries by mechanical trauma. Laryngeal contact and postintubation ulcers and granulomas are the consequence of mechanical trauma in the area of the vocal process of the arytenoid cartilage. It would be reasonable to assume that the use of zinc supplementation could significantly contribute to the treatment of this clinical entity. The effects of zinc on healing have been well documented, but they are not well understood. Clinical research is needed before coming up with valid recommendations and conclusions about the use of zinc supplementation in the treatment of laryngeal granuloma. Well-designed clinical trials are an absolute necessity before final conclusions can be drawn.

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

References

- Sun GB, Sun N, Tang HH, Zhu QB, Wen W, Zheng HL. Zinc sulfate therapy of vocal process granuloma. *Eur Arch Otorhinolaryngol* 2012; 269(9): 2087–90.
- Storck C, Brockmann M, Zimmermann E, Nekahm-Heis D, Zorowka PG. Laryngeal granuloma. Aetiology, clinical signs, diagnostic procedures, and treatment. *HNO* 2009; 57(10): 1075–80.
- Devaney KO, Rinaldo A, Ferlito A. Vocal process granuloma of the larynx—recognition, differential diagnosis and treatment. *Oral Oncol* 2005; 41(7): 666–9.
- Ylitalo R. A retrospective study of contact granuloma. *Laryngoscope* 1999; 109: 433.
- Tanić N, Milašin J, Dramićanin T, Bošković M, Vukadinović M, Milošević V, Tanić N. TP53 and C-Myc co-alterations – a hallmark of oral cancer progression. *J Med Biochem* 2013; 32: 380–8.
- Marshak A, Marshak G. Zinc sulfate therapy for vocal cord granulomas. *J Laryngol Otol* 1973; 87(6): 573–6.
- Yumoto E, Sanuki T, Miyamaru S, Kumai Y. Does subepithelial hemorrhage cause persistence of laryngeal granuloma? *Laryngoscope* 2008; 118(5): 932–7.
- Yilmaz T, Süslü N, Atay G, Ozer S, Günaydin RO, Bajin MD. Recurrent contact granuloma: experience with excision and botulinum toxin injection. *JAMA Otolaryngol Head Neck Surg* 2013; 139(6): 579–83.
- Mitchell G. Excision and low-dose radiotherapy for refractory laryngeal granuloma. *J Laryngol Otol* 1998; 112: 491.
- Pories WJ, Henzel JH, Rob CG, Strain WH. Acceleration of healing with zinc sulfate. *Ann Surg* 1967; 165(3): 432–6.
- Frassinetti S, Bronzetti G, Caltavuturo L, Cini M, Croce CD. The role of zinc in life: a review. *J Environ Pathol Toxicol Oncol* 2006; 25(3): 597–610.
- Bradbury S. Wound healing: is oral zinc supplementation beneficial? *Wounds UK* 2006; 54–8.
- Cereda E, Gini A, Pedrolli C, et al. Disease-specific, versus standard, nutritional support for the treatment of pressure ulcers in institutionalized older adults: a randomized controlled trial. *J Am Geriatr Soc* 2009; 57(8): 1395–402.
- Lin YS, Lin LC, Lin SW. Effects of zinc supplementation on the survival of patients who received concomitant

- chemotherapy and radiotherapy for advanced nasopharyngeal carcinoma: follow-up of a double-blind randomized study with subgroup analysis. *Laryngoscope* 2009; 119(7): 1348–52.
15. Collins N. Zinc supplementation: yea or nay? *Adv Skin Wound Care* 2003; 16(5): 226–30.
16. Tenaud I, Sainte-Marie I, Jumbou O, Litoux P, Dreno B. In vitro modulation of keratinocyte wound healing integrins by zinc, copper and manganese. *Br J Dermatol* 1999; 140(1): 26–34.
17. McLaren S. Nutrition and wound healing. *J Wound Care* 1992; (3): 45–55.
18. Agren MS. Zinc oxide increases degradation of collagen in necrotic wound tissue. *Br J Dermatol* 1993; 129(2): 221.
19. Sullivan DH, Sun S, Walls RC. Protein-energy undernutrition among elderly hospitalized patients: a prospective study. *JAMA* 1999; 281(21): 2013–19.
20. Kohn S, Kohn D, Schiller D. Effect of zinc supplementation on epidermal Langerhans' cells of elderly patients with decubital ulcers. *J Dermatol* 2000; 27(4): 258–63.
21. Pullen FW. Postintubation tracheal granuloma. *Archives of Otolaryngology* 1970; 92: 340.
22. Farwell DG, Belafsky PC, Rees CJ. An endoscopic grading system for vocal process granuloma. *J Laryngol Otol* 2008; 122(10): 1092–5.
23. Yilmaz T. Zinc sulfate treatment of vocal process granuloma. *Eur Arch Otorhinolaryngol* 2013; 270(3): 1175.

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