

Original research

Evaluation Of Anti-Inflammatory Effects Of Rosemary Extract In Reducing The Need For Dexamethasone In Intubation: A Randomized Clinical Trial

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Abstract

Introduction: Intratracheal intubation has many side effects in people who have difficulty intubating, the most common of which is hoarseness and sore throat; Therefore, it is necessary to prevent it. The aim of this study was to investigate the effects of rosemary on voice violence and sore throat after endotracheal intubation in women with difficult intubation.

Methods: This study was a randomized Non-blind clinical trial in which during 2018, with the participation of 70 patients undergoing general anesthesia, they were randomly (Randomly Permuted Block) divided into two groups: control (inserting sterile gauze impregnated with distilled water into the patient's throat) and intervention (inserting sterile gas impregnated with rosemary into the patient's throat). Sore throat and voice violence were measured using VAS scale and finally the data were entered in SPSS20 software and analyzed by descriptive and inferential statistics.

Results: The severity of sore throat in the intervention group ($49/77 \pm 4/77$) was not significantly ($p=0.6$) less than the severity of the control group ($53/20 \pm 4/93$); The need for treatment was not observed in either group.

Conclusion: Rosemary extract could not reduce noise and sore throat after intubation in people with difficult intubation.

Keywords: Intubation, hoarseness, sore throat, rosemary extract

Submitted: 17 November 2021, Revised: 21 February 2021, Accepted: 6 April 2021

Introduction

Intratracheal intubation is unavoidable following anesthesia and is directly related to

the type and length of surgery, the patient's condition, and the operating room conditions (1); Intratracheal intubation is a safe and

reliable method for oxygenation of patients who are to undergo surgery, and if done correctly, greatly reduces the stress and workload of the anesthesiologist and his assistant (2, 3).

Doing this properly requires scientific and principled training of medical students and other branches of the medical department. There are different methods for teaching endotracheal intubation and if done, it will enable and master people (4-6). Performing intubation intubation is not always easy (7); Because in about 1 to 8% of cases, intubation is a type of problem, and in people whose ovulation is a type of problem, the skill of the anesthesiologist can greatly calm the situation (8).

Problem intubation causes problems after laryngoscopy and more intubation than normal people, so that in some studies, the incidence of common complications after intubation is estimated to be up to three times higher than other people (9). Common complications after intubation include prolonged ventilation and increased risk of ventilator-associated pneumonia, increased induction and maintenance of anesthetics (10), increased duration of anesthesia and side effects of anesthetics (11), shortness of breath, ulcers And increase the severity of noise and sore throat (12). Meanwhile, voice violence and sore throat are more unpleasant and unbearable for many patients than postoperative pain, which increases the need for medication (13).

Sore throat (Incidence=35 %) and hoarseness (Incidence= 42 %) after endotracheal intubation for the reasons mentioned above have caused concern for anesthesiologists, so finding preventive methods to prevent this complication has always been a challenge for anesthesiologists (14); These concerns (Increased Sore throat and hoarseness incidence $\times 3$) become more difficult for people with intubation and increase the stress of the anesthesiologist as well as the need for postoperative medication and the need for more care in inpatient wards (8).

All the mentioned factors have caused preventive measures for these people to be considered by anesthesiologists more than medical procedures (15); There are several ways to do this, including ketamine gargling, corticosteroid use, different forms of lidocaine, beclomethasone inhalation, benzidamine hydrochloride spray, small endotracheal tube, intramuscular intubation and complete Chipping the tube when the cuff of the endotracheal tube is completely empty; All of these methods focus on reducing inflammation (14).

On the other hand, because each of the mentioned methods is followed with side effects and they have not been able to completely prevent noise and sore throat after intubation and reduce its rate to zero, use new methods and drugs that have the least side effects. It has always been considered in the studies of anesthesia professors and researchers (16). Rosemary plant due to its

compounds (carnosol and uricolic acid) has been able to be used as a good anti-inflammatory in most inflammatory diseases and has beneficial effects that no side effects have been reported so far; It has been approved by researchers and suggestions have been made to replace this plant with chemical drugs (which in most cases are associated with many side effects) (17). According to the recommendations to eliminate and reduce inflammation using rosemary (18), the researchers of the present study decided to reduce the anti-inflammatory effects of this substance to reduce and zero noise and sore throat after tracheal intubation in women. Which has a higher prevalence than men, to find the best way to eliminate the violence of the voice and sore throat after intubation, to avoid medication and its side effects.

Method

This study is a randomized clinical trial and Non-blinding that was conducted during 2017 and 2018 in Imam Reza (AS) Hospital affiliated to Tabriz University of Medical Sciences. Sample size was measured at 70 patients; The sample size was determined based on Cochran's formula with an error level of 5% and a population size of 80 patients (number of patients last year).

Samples were available by sampling method with compliance with inclusion criteria (patients 40-60 years old candidates for breast cancer surgery (total mastectomy) , patients with diagnosis of problem tubing with Malampati criteria (class III and IV) and

surgeries that require endotracheal intubation in supine position And withdrawal (use of anti-inflammatory drugs during the two weeks before surgery, history of upper airway infection and sore throat, prolongation of the operation more than 4 hours, daily allergies, drug addiction, psychopathy of the patient, emergency patients)

After obtaining informed written consent, approval in the ethics committee of Tabriz University of Medical Sciences and registration in the clinical trial system with the code IRCT20180806040724N1 were included in the study. Also, patients were randomly divided into four groups of 35 control and intervention by random 4 and random randomized method (Randomly Permuted Block) and using the relevant software from www.randomization.org. All the necessary ethical considerations were observed in this study as in similar studies.

Cardiovascular, endocrine, internal medicine and forensic consultations were performed for all patients, the anesthesiologist visited the patients one day before the surgery and examined the patients for the difficulty of endotracheal intubation. Half an hour before transferring patients to the operating room, 500cc of normal saline was given through IV line implanted with angiocatheter number 20 to hydrate patients. After entering the operating room, anesthesia monitoring (pulse oximetry, ECG and peripheral blood pressure) was performed for all patients. Patients were

then pretreated with 1-2 mg / kg of fentanyl and 0.02 mg / kg of midazolam and induction with propofol 2.5-1 mg / kg and atracurium at a dose of 0.5 mg / kg. Kg and lidocaine 2% were given 1-1.5 mg per kg and after 3 minutes, the patient was gently intubated by an anesthesiologist to ensure complete muscle relaxation with a 7 mm diameter orthopedic tube. After intubation, a sterile gas impregnated with the study fluid was placed in the patient's pharynx with the help of forceps. These gases were prepared by the relevant technician who entered during the investigation, so that the gases of the intervention group were impregnated with 3CC of rosemary syrup of Fadak Sepahan Farm Pharmaceutical and Agro-Industrial Company, generic *R. officinalis* (containing rosemary extract). ; Control gases were also impregnated with 3CC of distilled water; The surgeon and anesthesiologist, as well as the patients, were unaware of the gaseous fluid. Continued anesthesia was administered by TIVA with propofol and remifentanyl. Vital signs of all patients were kept within the normal range and changes in vital signs of more than ten percent removed the samples from the study process.

At the end of the operation, muscle relaxation was reversed with neostigmine (0.05 mg / kg) and atropine (0.04 mg / kg); Gas was removed from the patients's mouth and the patient's endotracheal tube was removed after suctioning the secretions into the mouth and the patients were transferred to the recovery

unit. After the patient regained consciousness, the patient's sore throat was measured and recorded using VAS scale by a medical student who was unaware of the grouping in recovery and 2-6-24 hours after that. The same analgesic regimen was used in the analgesia ward. (50 mg intravenous pethidine) was used for all patients. Dexamethasone 4 mg was injected as IM if severe sore throat required medical treatment.

Data obtained from the study by descriptive statistical methods (frequency, percentage, mean and standard deviation), mean difference test for independent groups and repeated measures RMA design test and chi-square relationship test or Fisher's exact test using SPSS20 was statistically analyzed. $P < 0.05$ was considered significant. The normality of data distribution was assessed by Kolmogorov-s test and Q-Q diagram.

Results

In this study, the number of participants was 70 who were divided into two equal groups of 35 intervention and control. The mean duration of general anesthesia for surgery was $110/45 \pm 26/45$ Min and the mean age of patients participating in the study was $42.70 \pm 14/05$ years. Detailed information for each group is given in Table 1. The number of patients with postoperative sore throat in patients receiving rosemary herbal medicine was 66 in total and in the control group was 72. There was no significant difference between the two groups ($p = 0.6$).

Table 1: Basic information of patients participating in the study

Variable	Control (N=35)	Intervention (N=35)	P Value
Age	43.99±6.89	42.21±5.99	p=0.89
Anesthesia Time (Min)	119.71±13.88	111.28±12.74	p=0.137

Number of people had sore throat after anesthesia It is given in Table 2 at different times. In general, the mean pain intensity in all hours after anesthesia in the intervention group was 1/91±0/85 and in the control group was 1/77±0/97, which was not statistically significant ($p = 0.88$); Pain intensity in recovery and 2-6-12-24 hours in two groups are given in Table 3. Since severe sore throat was not observed in any of the patients, dexamethasone was not injected in any group.

Table 2: Patients with sore throat after anesthesia were measured at different times

Time	Intervention (N=35)	Control (N=35)	P Value
In Recovery	9	13	0.452
2 hours after recovery	11	16	0.149
6 hours after recovery	9	12	0.219
12 hours after recovery	10	15	0.316

24 hours after recovery	10	14	0.385
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Discussion

The aim of the present study was to evaluate the effects of rosemary on voice and sore throat after endotracheal intubation in women with difficult intubation. Problem intubation is one of the most difficult and stressful procedures for anesthesiologists and due to the problem of laryngoscopy, these people are more likely to develop inflammation after intubation (8); Inflammation after intubation causes sore throat and hoarseness, so following the increase in inflammation and the likelihood of sore throat and complaints of patients after anesthesia, medication and preventive measures are taken by anesthesiologists to deal with this problem; Several medications are taken after the patient leaves the operating room, in most of which the effect does not significantly reduce sore throat and hoarseness. On the other hand, in people who have problems with intubation, the severity of the inflammation is sometimes so great that there is a need to prescribe several drugs (25, 26); Therefore, preventive action is welcomed by anesthesiologists as well as patients, because patients in this condition do not experience sore throat and violence to need medication, which increases the acceptance of patients to prevent sore throat (27).

Since rosemary extract has not been used to prevent hoarseness and sore throat after intubation and this study is the first study in this field, researchers compare the results of this study with the anti-inflammatory effects of this extract in other diseases. . In a study conducted by Rocha et al. To investigate the anti-inflammatory effects of rosemary extract, researchers found positive and beneficial effects of this extract in severely reducing inflammation in their study (28); The anti-inflammatory and antioxidant effects of carnosol as one of the substances in rosemary extract have potential effects in reducing inflammation and it seems that the severe reduction in inflammation in the study of Rocha et al. Is due to this substance. Ms Rahbardar et al. In their study conducted in an animal model found positive anti-inflammatory effects of this extract in reducing inflammation in neuropathic pain (29) whose results are not consistent with the present study.

In the study, the effects of antioxidants such as rosemary extract on reducing diabetic neuropathy were mentioned. The researcher believes that the antioxidants in rosemary herbs can reduce inflammation and neuropathic pain in diabetics. The results of his study on the positive anti-inflammatory effects of rosemary extract are not in line with the results of the present study and are not in the same direction (30). In a study by Brady et al., The positive and beneficial effects of rosemary extract on reducing the excitability

of nerve cells have been mentioned and it is believed that the extract of this plant due to its antioxidant and anti-inflammatory effects can greatly reduce cell stimulation. The central nervous system (31); The positive results observed in their study are not in line with the lack of positive effect of using this extract in intubation. Ghafarzadegan et al. In their study observed the positive effects of ointment composed of rosemary extract to reduce back pain after coronary angiography and state that the use of this extract, in addition to being welcomed by the patient, has positive and appropriate effects on The reduction of back pain is after surgery (32), the results of their study are not in line with the results of the present study and are not in the same direction.

The low concentration of rosemary extract in this study and the lack of use of this drug before intubation is a weakness of the present study, as well as the lack of accurate information about the purity of this substance as a limitation of the present study. Lack of attention to the time spent for intubation and the number of times for intubation The problem is the weakness of the present study and researchers suggest conducting further studies to investigate the effects of this drug in gel form. Due to the lack of positive effect of rosemary extract, researchers consider the use of this substance to reduce sore throat after intubation, useless.

Conclusion

Rosemary extract, which has proven anti-inflammatory effects, could not reduce sore throat and hoarseness in people with intubation due to the absence of any side effects in the present study.

Acknowledgments

This support of Tabriz University of Medical Sciences (Code number of ethics: IR.TBZMED.REC.1397. 252). Hereby, the researcher expresses his sincere gratitude to the university faculty members who collaborated on the construction of this questionnaire.

References

1. Bouabdallaoui N, Stevens SR, Doenst T, Wrobel K, Bouchard D, Deja MA, et al. Impact of intubation time on survival following coronary artery bypass grafting: Insights from the Surgical Treatment for Ischemic Heart Failure (STICH) trial. *Journal of cardiothoracic and vascular anesthesia*. 2018;32(3):1256-63.
2. Ghanei Gheshlagh R, Dastras M, Fazlali PourMiyandoab M, Naseri O. The relationship between preoperative anxiety and postoperative nausea and vomiting. *Med Sci J*. 2014;23(4):269-74.
3. Sabzalizadeh S, Ravaghi H, Salehi M, Delshad V. The effectiveness Comparison of palonosetron with ondansetron in preventing postoperative nausea and vomiting in patient undergoing general anesthesia: A Meta-analysis and Systematic review. *Anesth Pain*. 2016;6(4):66-76.

4. Aghamohammadi D, Farzin H, Gol MK. The Effect of intubation training on the success of cardiopulmonary resuscitation in medical students -2015. *Iranian Journal Of Anaesthesiology and Critical Care*. 2018;2(2):51-8.
5. Aghamohammadi D, Farzin H, Fakhari S, Gol MK. The comparison of simulated endotracheal intubation training on mannequin and normal patient in medical students of Tabriz University of Medical Sciences -2015. *Iranian Journal Of Anaesthesiology and Critical Care*. 2018;2(3):44-53.
6. Eskandarian T, Baghi S, Alipoor A. Comparison of clinical success of applying a kind of fissure sealant on the lower permanent molar teeth in dry and wet conditions. *Journal of Dentistry*. 2015;16(3):162.
7. Hakim R, Watanabe Tejada L, Sukhal S, Tulaimat A. A Systematic Review of the Criteria for Endotracheal Intubation for Mechanical Ventilation in Randomized Trials. *C49 CRITICAL CARE: EVERY BREATH YOU TAKE-ACUTE RESPIRATORY FAILURE AND MECHANICAL VENTILATION: American Thoracic Society*; 2018. p. A5134-A.
8. Frerk C, Mitchell V, McNarry A, Mendonca C, Bhagrath R, Patel A, et al. Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. *BJA: British Journal of Anaesthesia*. 2015;115(6):827-48.
9. Soleimani S, Mofrad F, Kareshki H. Interpersonal Emotion Regulation

- Questionnaire (IERQ) in Persian speaking population: adaption, factor structure and psychometric properties. *International Journal of Applied Behavioral Sciences*. 2018;3(4):42-9.
10. De Jong A, Molinari N, Pouzeratte Y, Verzilli D, Chanques G, Jung B, et al. Difficult intubation in obese patients: incidence, risk factors, and complications in the operating theatre and in intensive care units. *British journal of anaesthesia*. 2014;114(2):297-306.
 11. Nørskov A, Wetterslev J, Rosenstock C, Afshari A, Astrup G, Jakobsen J, et al. Effects of using the simplified airway risk index vs usual airway assessment on unanticipated difficult tracheal intubation—a cluster randomized trial with 64,273 participants. *BJA: British Journal of Anaesthesia*. 2016;116(5):680-9.
 12. Hagberg C, Gabel JC, Connis R. *Difficult Airway Society 2015 guidelines for the management of unanticipated difficult intubation in adults: not just another algorithm*. Oxford University Press; 2015.
 13. Tanaka Y, Nakayama T, Nishimori M, Tsujimura Y, Kawaguchi M, Sato Y. Lidocaine for preventing postoperative sore throat. *Cochrane database of systematic reviews*. 2015 (7).
 14. El-Boghdadly K, Bailey C, Wiles M. Postoperative sore throat: a systematic review. *Anaesthesia*. 2016;71(6):706-17.
 15. Cirilla II DJ, Ngo J, Vaisman V, Daly C, Ata A, Sandison M, et al. Does the incidence of sore throat postoperatively increase with the use of a traditional intubation blade or the GlideScope? *Journal of clinical anesthesia*. 2015;27(8):646-51.
 16. Hoare KJ, Ward E, Arroll B. International sore throat guidelines and international medical graduates: a mixed methods systematic review. *Journal of primary health care*. 2016;8(1):20-9.
 17. Topal M, GÜLÇİN İ. Rosmarinic acid: a potent carbonic anhydrase isoenzymes inhibitor. *Turkish journal of chemistry*. 2014;38(5):894-902.
 18. Nunes S, Madureira AR, Campos D, Sarmiento B, Gomes AM, Pintado M, et al. Therapeutic and nutraceutical potential of rosmarinic acid—Cytoprotective properties and pharmacokinetic profile. *Critical reviews in food science and nutrition*. 2017;57(9):1799-806.
 19. Linos E, Willett WC, Cho E, Frazier L. Adolescent diet in relation to breast cancer risk among premenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2010;19(3):689-96.
 20. MacCallum RC, Widaman KF, Zhang S, Hong S. Sample size in factor analysis. *Psychol Methods*. 1999;4(1):84.
 21. Felder L, Saccone G, Scutto S, Monks DT, Carvalho JC, Zullo F, et al. Perioperative gabapentin and post cesarean pain control: a systematic review and meta-analysis of randomized controlled trials. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2019;233:98-106.

22. Baghi S, Amareh M, Heirat R, Hajivandi A, Aalizadeh Y. Evaluation of relationship between the children's dental fear and cooperation during dental treatment with the parents' general health. *Iranian Journal of Pediatric Dentistry*. 2018;13(2):37-42.
23. Maitra S, Baidya DK, Bhattacharjee S, Som A. Perioperative gabapentin and pregabalin in cardiac surgery: a systematic review and meta-analysis. *Revista brasileira de anestesiologia*. 2017;67(3):294-304.
24. Kang J, Zhao Z, Lv J, Sun L, Lu B, Dong B, et al. The efficacy of perioperative gabapentin for the treatment of postoperative pain following total knee and hip arthroplasty: a meta-analysis. *Journal of Orthopaedic Surgery and Research*. 2020;15(1):1-9.
25. Wang T, Sun S, Huang S. The association of body mass index with difficult tracheal intubation management by direct laryngoscopy: a meta-analysis. *BMC anesthesiology*. 2018;18(1):79.
26. Hashim MM. Difficult tracheal intubation in bariatric surgery patients, a myth or reality? *BJA: British Journal of Anaesthesia*. 2015;115(eLetters Supplement).
27. Zhao X, Cao X, Li Q. Dexamethasone for the prevention of postoperative sore throat: a systematic review and meta-analysis. *Journal of clinical anesthesia*. 2015;27(1):45-50.
28. Rocha J, Eduardo-Figueira M, Barateiro A, Fernandes A, Brites D, Bronze R, et al. Anti-inflammatory effect of rosmarinic acid and an extract of *Rosmarinus officinalis* in rat models of local and systemic inflammation. *Basic & clinical pharmacology & toxicology*. 2015;116(5):398-413.
29. Rahbardar MG, Amin B, Mehri S, Mirnajafi-Zadeh SJ, Hosseinzadeh H. Anti-inflammatory effects of ethanolic extract of *Rosmarinus officinalis* L. and rosmarinic acid in a rat model of neuropathic pain. *Biomedicine & Pharmacotherapy*. 2017;86:441-9.
30. Tavafi M. Diabetic nephropathy and antioxidants. *Journal of nephropathology*. 2013;2(1):20.
31. Braidy N, Martin A, Rossi F, Chinain M, Laurent D, Guillemin G. Neuroprotective effects of rosmarinic acid on ciguatoxin in primary human neurons. *Neurotoxicity research*. 2014;25(2):226-34.
32. Ghafarzadegan R, Noruzi M, Mousavi M, Alizadeh Z, Harorani M, Javaheri J. The Effect of a Combined Herbal Ointment (Pepper, Rosemary, Peppermint) on Low back Pain after Coronary Angiography. *Journal of Medicinal Plants*. 2018;4(64):76-82.
- review and meta-analysis. *Revista brasileira de anestesiologia*. 2017;67(3):294-304.
43. Kang J, Zhao Z, Lv J, Sun L, Lu B, Dong B, et al. The efficacy of perioperative gabapentin for the treatment of postoperative pain following total knee and hip arthroplasty: a meta-analysis. *Journal of Orthopaedic Surgery and Research*. 2020;15(1):1-9.