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The Role of Zinc in the Prevention and Treatment of Dysgeusia in Head and Neck Cancer Patients Receiving Radiotherapy or Chemoradiotherapy: A Case Study with Evidence-Based Approaches

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ABSTRACT

Background: Despite its significant impact on nutrition status, there is no therapy modality proven to be effective in the prevention and treatment of dysgeusia to date. Zinc is known for its important role in the function of taste buds, however the effect of zinc supplementation in dysgeusia related to radiotherapy or chemoradiotherapy is still on research.
Objective: This study aimed to evaluate role of zinc in the prevention and treatment of dysgeusia in head an neck cancer patients receiving radiotherapy or chemoradiotherapy.
Method: This study used literature search on Pubmed, Cochrane Library, and ProQuest databases to retrieve SR-MA and RCT articles that fit the clinical question of this case study.
Result: One SR-MA and one RCT article were critically appraised. The SR-MA of 5 RCT studies (n=272) found that zinc based therapy reduces the incidence of dysgeusia related to radiotherapy or chemoradiotherapy (RR 0,79; 95% CI, 0,67 – 0,92), but it had no effect on ongoing dysgeusia (RR 2,58; 95% CI, 0,97 – 6,88). Meanwhile, the RCT study (n=68) demonstrated no beneficial effect of zinc supplementation on the prevention and treatment of dysgeusia related to radiotherapy or chemoradiotherapy.
Conclusion: Zinc supplementation may be beneficial for the prevention of dysgeusia in head and neck cancer patients receiving radiotherapy or chemoradiotherapy despite its finding on researchs remain inconclusive. More high quality RCTs are needed to confirm the effectivity of zinc at preventing and improving dysgeusia in head an neck cancer patients receiving radiotherapy or chemoradiotherapy.

Keywords: zinc, dysgeusia, radiotherapy, chemoradiotherapy, head and neck cancer

INTRODUCTION

Being the 7th most common cancer among all cancer cases, head and neck cancer contributes to 890.000 new cases and 450.000 death annually.[1] As the patients receiving radiotherapy which most of the time combined with chemotherapy as the anticancer modality, some adverse effects are experienced by the patient.[2,3] Dysgeusia is one of the most common adverse effect affected head and neck cancer patients during radiotherapy or in combination with chemotherapy.[4] It develops due to destruction of cells in the taste buds that

exposed to radiation beam starting from cumulative dose of 20 Gy. At even higher cumulative dose of 50 – 70 Gy, about 70 – 85% patients will develop grade 1 dysgeusia (taste disturbance with no change in diet), and 55% will develop grade 2 dysgeusia (taste disturbance with a change in diet, unpleasant taste, and loss of taste).[4]

Dysgeusia followed change in diet results in decreased food intake and eventually increases the risk or even worsen malnutrition in head and neck cancer patients who are already nutritionally compromised by the cancer itself.[5,6,7] Besides, it's not uncommon that head and neck cancer patients also suffer from other concomitant oral cavity complications related to chemoradiotherapy such as mucositis, xerostomia, odynophagia and dysphagia that affected their food intake and leading to weight loss in malnutrition.[2,3] Malnutrition in cancer patient is associated with longer hospital stay, decreased quality of life, and negatively impact the effectivity of anticancer therapy, thus worsening the prognosis.[8,9] Many patients reported gradual improvement in dysgeusia within 6 – 12 months but there is also association between elevated oral pain and dysgeusia found during the 5-year of survival in head and neck cancer patients.[4]

Zinc is one of micronutrients that has important role in many functions in human including function of taste buds.[10] It has been discovered that decreased level of salivary zinc is associated with decreased level of gustin, which is the major zinc-containing protein in human parotid saliva. Its decreased level is linked to abnormality of growth and development of taste buds and also loss of taste. Patients with hypogeusia are found to have low level of salivary zinc and significantly altered shape of taste buds.[10] Several studies have been conducted to evaluate the effectivity of zinc supplementation at preventing and improving dysgeusia related to radiotheraphy or chemoradiotherapy in head and neck cancer patients. However, the findings are still inconsistent from one study to another.[4,11] Difference in sample size, assessment method of dysgeusia, and type of anticancer exposure are considered as the factors that contributes to the inconsistency of the research findings.[4,11]

Since the symptoms sometimes are not severe enough to cause disturbance in daily life, some patients might not report their complaints of dysgeusia, thus proper medical care cannot be delivered to the affected patients. As dysgeusia increases the risk of malnutrition and it is linked to worse outcomes in head and neck cancer patients, a literature search aiming for high quality evidences is required to answer the clinical question about the role of zinc in the prevention and treatment of dysgeusia in head a neck cancer patients receiving radiotherapy or chemoradiotherapy.

CASE REPORT

A 60 year old male patient diagnosed with *Extranodal NK-T cell lymphoma, nasal type* was referred to Nutrition outpatient clinic Dr. Cipto Mangunkusumo General Hospital from Oncology-Radiation outclinic patient as he was screened at risk for malnutrition with a MST score of 3. During the first visit, the patient reported decreased appetite but without any disturbances in the oral cavity that could affect his food intake. Patient was planned to receive IMRT (*Intensity Modulated Radiation Therapy*) with a cumulative dose of 30x1,8 Gy and 5 cycles of concurrent chemotherapy with a weekly regimen of cisplatin 30 mg/m^2 continued with 3 cycles of VIPD (*etoposide*, ifosfamide, cisplatin, and dexamethasone). During the 5th visit, after completing 18 fraction of radiotherapy and 3 cycles of chemotherapy, patient complained a symptom of dysgeusia, resulting in the reduction of food intake due to worsening of appetite. The complaint was continuously reported until the end of the chemoradiotherapy. Dysgeusia is one of the well-known adverse effects of radiotherapy with or without chemotherapy experienced by head and neck cancer patients. Some low quality studies with unclear risk of bias

suggest the supplementation of one 45 mg zinc sulfate tablet by mouth three times daily at the start of radiotherapy and continued for 4 weeks after completion of radiotherapy to prevent dysgeusia. Stronger evidence is needed to make this regimen adopted into daily clinical practice.

CLINICAL QUESTION

"Is zinc supplementation effective at preventing and treating dysgeusia in head and neck cancer patients receiving radiotherapy or chemoradiotherapy?"

Participants (P): adult head and neck cancer patients receiving radiotherapy or chemoradiotherapy

Intervention (I): zinc supplementation

Control (C): placebo

Outcome (O): lowered incidence and improvement of dysgeusia

METHODS

Searching strategy

The literature search was conducted on 3 databases including PubMed, Cochrane Library, and ProQuest, by using advanced searching on the combination of the following free text keywords and Medical Subject Heading (MeSH) terms: "zinc", "dysgeusia", "ageusia", "hypogeusia", ,"taste alteration", "taste change", "taste disturbance", "neoplasm, head and neck", "cancer of head and neck", "radiotherapy", chemotherapy", chemoradiotherapy", "radiochemotherapy". The literature search strategy is presented in table 1. The retrieved articles then screened for duplication and asessed for the PICO's similarity with this case study. Articles that fit the clinical question of this case study were included for critical appraisal using tools from CEBM (Centre for Evidence Based Medicine).

Eligibility Criteria

Inclusion criteria: 1) study participants were adult head and neck cancer patients planned to or in the middle of receiving radiotherapy or chemoradiotherapy; 2) intervention was zinc supplementation versus placebo; 3) outcomes are incidence or improvement of dysgeusia related to radiotherapy or chemoradiotherapy; 4) articles of systematic review-meta-analysis (SR-MA) of randomized controlled trials (RCT) and RCT study.

Exclusion criteria: 1) study that uses zinc supplementation as a part of combined intervention with other modalities; 2) articles published in languages other than English and Indonesia language; 3) on going study; 4) articles without accessible full-text.

Table 1. Literature search strategy

Database	Search strategy		Hits
Pubmed	((((zinc[Title/Abstract]) OR (zinc[MeSH Terms])) AND ((((head[Title/Abstract] AND neck cancer[Title/Abstract]) OR (head and neck cancer[MeSH Terms])) OR (head[Title/Abstract] AND neck neoplasms[Title/Abstract])) OR (head and neck neoplasms[MeSH Terms])))) AND (((((((radiotherapy[Title/Abstract]) OR (radiotherapy[MeSH Terms])) OR (chemotherapy[Title/Abstract])) OR (chemotherapy[MeSH Terms])) OR (chemoradiotherapy[Title/Abstract])) OR (chemoradiotherapy[MeSH Terms])) OR (radiation[Title/Abstract])) OR (radiation[MeSH Terms])))) AND ((((((((((dysgeusia[Title/Abstract]) OR (dysgeusia[MeSH Terms])) OR (taste disturbance[Title/Abstract]))) OR (taste disturbance[MeSH Terms])) OR (taste alterations[Title/Abstract])) OR (taste alterations[MeSH Terms])) OR (taste buds[Title/Abstract])) OR (taste buds[MeSH Terms])) OR (ageusia[Title/Abstract])) OR (ageusia[MeSH Terms])) OR (hypogeusia[Title/Abstract])) OR (hypogeusia[MeSH Terms]))		8
Cochrane Library	ID	Search Hits	8
	#1	(neoplasm of head): ti,ab,kw AND (neck):ti,ab,kw OR (cancer of head):ti,ab,kw AND (neck):ti,ab,kw	
	#2	(radiation):ti,ab,kw OR (radiotherapy):ti,ab,kw OR (chemotherapy):ti,ab,kw OR (chemoradiotherapy):ti,ab,kw OR (radiochemotherapy):ti,ab,kw	

	#3	(zinc):ti,ab,kw OR (topical zinc):ti,ab,kw OR (zinc sulfate):ti,ab,kw OR (polaprezinc):ti,ab,kw	
	#4	(dysgeusia):ti,ab,kw OR (taste disturbance):ti,ab,kw OR (taste alterations):ti,ab,kw OR (ageusia):ti,ab,kw OR (hypogeusia):ti,ab,kw	
	#5	#1 AND #2 AND #3 AND #4	
Proquest	((title(zinc) OR title (zinc sulfate)) AND (title(dysgeusia) OR title (taste alterations) AND title (taste disturbances) OR title (taste buds) OR title (ageusia) OR title (hypogeusia)) AND (title(radiation) OR title(radiotherapy) OR title(chemotherapy) OR title(chemoradiotherapy)))		2

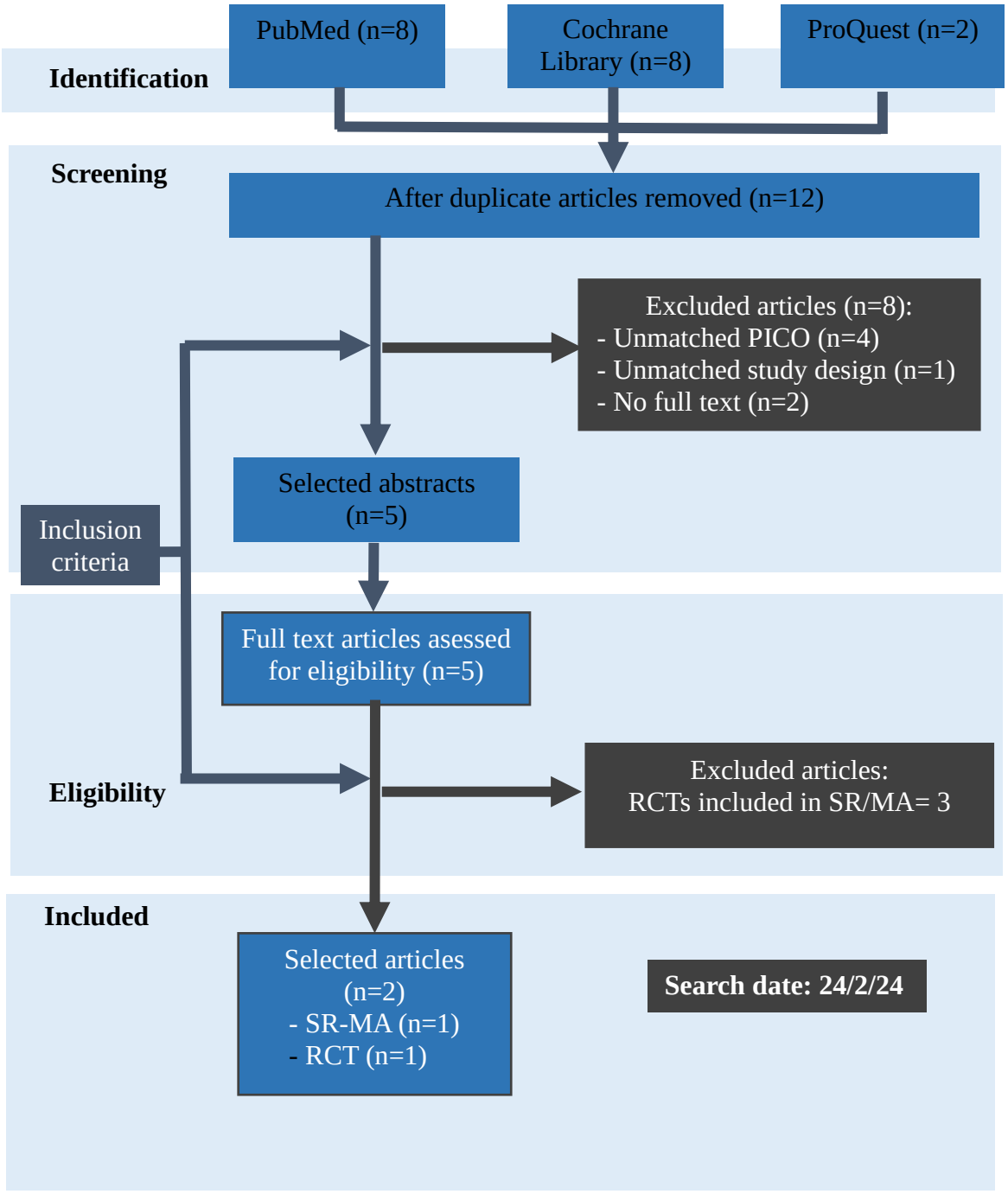

Figure 1. The flow diagram of literature search

RESULT

The flow diagram of the literature search is illustrated in Fig. 1. Eighteen articles were initially identified from the 3 databases. After removing 6 duplicate articles, 12 articles were screened for eligibility based on abstract and full text. There were 3 RCT articles already included in a SR-MA article thus they were excluded. Finally, 2 full text articles of 1 SR-MA and 1 RCT article were selected for the critical appraisal. Characteristic of selected articles in presented in table 2. The selected articles were critically appraised to review the validity, importance and applicability. Summary of critical appraisal result of each article is presented in table 3 and 4.

Article	Study Design	Population	Intervention	Outcome
Chi W J et al. (2021)[4]	Systematic Review & Meta Analysis of randomized controlled trial	5 RCTs (N=272), head and neck cancer patients undergoing radiotherapy, chemotherapy, or combination of both at a hospital or university medical center.	116 subjects of 5 RCTs received: 1) one 50 mg zinc sulfate capsule by mouth 3 times daily; 2) oral rinse with 0,5 g polaprezinc in 20 mL of 5% sodium alginate for 3 minute/- swallow 4 times daily; 3) one 45 mg zinc sulfate tablet by mouth three times daily; 4) One 18 mg zinc sulfate tablet by mouth 4 times daily, while the rest 156 subjects received placebo	Incidence and improvement of dysgeusia
Khan A H et al. (2019)[11]	Double blind randomized controlled trial	N=68, oral cancer patients who were about to receive concurrent chemotherapy with radiotherapy for the first time, both gender aged between 20 to 60 years with radiation planned between 60 – 70 Gy of external beam radiotherapy and Cisplatin given as primary chemotherapeutic agent.	34 subjects received one 50 mg zinc sulfate 3 times a day, while the rest 34 subjects received placebo	Incidence and improvement of dysgeusia

Table 2. Characteristic of selected articles

Table 3. Summary of critical appraisal result of a SR-MA article by Chi W J et al

	Study Design	Question	Find	Appraise	Inclusion	Total Up	Heterogeneity	Result	Applicability	Level of Evidence
Chi W J et al. (2021)[4]	Systematic Review & Meta Analysis of randomized controlled trial	+	+	+	Unclear	+	Unclear	A	+	Level 1a

A: Compared with placebo, zinc reduced the incidence of radiotherapy/chemoradiotherapy induced dysgeusia (RR, 0.79; 95% CI, 0.67–0.92), but no effect on ongoing radiotherapy/chemoradiotherapy induced dysgeusia (RR, 2.58; 95% CI, 0.97–6.88)

Table 3. Summary of critical appraisal result of a RCT article by Khan A H et al

	Study Design	Randomization	Similarity	Equally treated	Intention to treat analysis	Blinding	Result	Applicability	Level of Evidence
Khan A H et al. (2019)[11]	Double blind randomized controlled trial	+	+	+	+	Double blind	B	+	Level 1b

B: there was statistically significant difference for median recognition threshold (RT) for sweet taste at the end of concurrent chemoradiotherapy (CCRT) and follow-up, and median RT for sour taste at the end of CCRT between control and intervention group. No significant difference for the median DT (detection threshold) or RT of other tastes observed between the 2 groups.

DISCUSSION

Literature search provided 1 SR-MA article and 1 RCT article to answer the clinical question about the effectivity of zinc supplementation at preventing and treating dysgeusia in head and neck cancer patients receiving radiotherapy or chemoradiotherapy. Critical appraisal conducted for the articles showed that the SR-MA by Chi W J et al had some uncertainties in validity as the study included RCTs with unclear risk of bias and there was no clear explanation about the cause of heterogeinity in their datas. Meanwhile, the RCT by Khan A H et al study did not present the confidence interval of their findings that could help estimating the therapy effect if it was applied in the population, thus it put some questions for the importance of the study's result.

Chi W J et al conducted 2 separate meta-analysis on the RCTs they collected for the SR-MA. They found that zinc based therapy could reduce the incidence of dysgeusia (RR 0,79; 95% CI, 0,67 – 0,92), but had no effect on ongoing dysgeusia (RR 2,58; 95% CI, 0,97 – 6,88) in head and neck cancer patients receiving radiotherapy or chemoradiotherapy.[3] Based on data they presented in a forest plot, a RCT by Halyard et al had the biggest weight (76,37%) among the 3 studies meta-analysed for the effect of zinc on radiotherapy or chemoradiotherapy induced dysgeusia.[3] The participants of the RCT received one 45 mg zinc sulfate tablet 3 times daily from within 7 days of the initiation of radiotherapy until 4 weeks after radiotherapy completion (some participants also received concomitant chemotherapy).[3,12] However, Chi W J et al stated that a firm conclusion could not be drawn from the findings of their study due to the RCTs they analyzed had small number of subjects and were considered limited that could obscure the true findings.[3] On the other hand, the RCT of Khan A H et al demonstrated that supplementation of one 50 mg zinc sulfate tablet 3 times daily had no beneficial effect on the prevention of chemoradiotherapy-induced dysgeusia.[11] The study could only obtain the statistically significant difference for the median RT (*recognition threshold*) of sweet taste at the end of CCRT (concurrent chemoradiotherapy) and follow-up, and for the median RT of sour taste at the end of CCRT between the intervention and control group. No significant difference for the median DT (detection threshold) and RT of other tastes observed between the 2 groups. The authors claimed that the short follow-up duration could be the limitation of this study since the long term effect and safety of zinc supplementation could not be studied.[11]

Both eligible SR-MA and RCT selected for this case study reported no effect of zinc supplementation on ongoing dysgeusia in head and neck cancer patients receiving radiotherapy or chemoradiotherapy.[3,11] Eventhough this finding is not explicitly concluded as the result of the RCT by Khan et al, but from the result of data analysis, it could be seen that no significant difference found between all median DT and RT except for the sweet taste on the measurement at 3 months of follow-up.[11] Whereas, significant difference found on the median RT of sweet taste favors the control group, therefore zinc supplementation failed to show better outcome in the intervention group compared with placebo group. This study showed that sweet taste was most affected among all tastes for both groups.[11] One of factors that determines the quality of taste disturbance in patients experienced dysgeusia is the difference on the exposed area of the tongue to radiation.[13] A study by Zheng at al indicated that the group who had received radiation on the anterior part of their tounge where the fungiform papillae are at the highest number experienced worse disturbance of sweet taste compared with a group who did not receive radiotherapy on that area.[13]

Zinc supplementation for head and neck cancer patients receiving radiotherapy or chemoradiotherapy does not fully show no beneficial effect. SR-MA by Chi W J et al however obtained possitive effect of zinc

supplementation on the prevention of dysgeusia, eventhough this finding is contradictive to the finding of RCT by Khan A H et al.[3,11] Khan A H et al explained that the difference between one study to another could be caused by the different type of anticancer exposure received by the patients in each study. Two of 3 RCTs analyzed for zinc supplementation effect on the incidence of dysgeusia in SR-MA by Chi W J et al did the recearch on head and neck cancer patients who received radiotherapy combined with chemotherapy but did not mentioned the type of chemotherapeutic agent given to the patients.[12,14,15] Whereas, RCT by Khan et al was conducted on head and neck cancer patients who received cisplatin as the chemoterapeutic agent concurrent with radiotherapy.[11] It has been known that platinum agent such as cisplatin may cause alteration in taste and smell perception by generating neurotoxic damage at receptor cells.[16,17] A study on gastrointestinal cancer patients reported higher incidence of dysgeusia in the group receiving platinum based chemotherapy compared with the group receiving non cisplatin based chemotherapy. Moreover, zinc supplementation in the group receiving platinum agent showed no effect at improving taste function eventhough there was an increase in serum zinc level.[18]

Another factor that contributes to the inconsistency of findings among studies is the difference of methods used to asess the taste function. RCT studies of the SR-MA by Chi W J et al used CTCA (Common Terminology Criteria for Adverse Events), Wickham Questionnaire, or research survey that was customized with a specific focus at the effect of zinc on dysgeusia. Meanwhile, the RCT by Khan et al adopted ISO Method to investigate the sensitivity of taste. The difference in assessment method might cause the difference in the incidence and improvement of dysgeusia observed by the studies.[3,11]

The 2 articles present different result from one to another, therefore a conclusive statement could not be drawn to answer the clinical question of this case study. However, there is an evidence from the SR-MA that zinc supplementation at the start of radiotherapy or chemoradiotherapy is beneficial to prevent dysgeusia in head and neck cancer patients. The regimen used in the study that could be adopted to daily practice is one 45 mg zinc sulfate tablet 3 times daily.[3,12] More RCT studies with bigger sample size, clear disclosure of radiotherapy and chemotherapy regimen, and standardized method of outcome measurement are required to provide better evidences to evaluate the effectivity of zinc at preventing and improving dysgeusia in head a neck cancer patients receiving radiotherapy or chemoradiotherapy.

CONCLUSION

Conclusive answer of the clinical question of this study could not be drawn yet, however there is potential beneficial effect of zinc supplementation at preventing dysgeusia in head and neck cancer patients receiving radiotherapy or chemoradiotherapy supported by a SR-MA. More RCT studies with better quality are required to collect stronger evidences for answering the clinical question of this case study in the future.

Declaration by Authors

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