ORIGINAL ARTICLE

Interventions for the treatment of Radiotherapy Induced Trismus: A Systematic Review of the Literature

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OBJECTIVES: To systematically assess the outcome of interventions used to treat patients who have trismus as a result of radiotherapy to the head and neck region in the treatment of Head and Neck Cancer (HNC).
METHODOLOGY: Searches were carried out on online databases (Medline, Embase and The Cochrane Central Library) on the 19th of June 2019 and then again using the same search terms on the 6th of June 2021. Randomized and Non-Randomized trials aimed at treating trismus as a side effect of head and neck radiotherapy (RT) were included for this systematic review. A total of 5 papers were reviewed for the purpose of this systematic review.
RESULTS: Results show that there is limited evidence to support the use of any treatment modality other than structured jaw exercises to help treat trismus in patients with a history of HNC and RT induced fibrosis. There is no evidence to support the use of Botulinum toxin A, while further studies are needed to clarify the effectiveness of Pentoxifylline (with or without conjunction with Vitamin E) and Pregabalin in the treatment of postradiotherapy fibrosis.
CONCLUSION: There is a need for more randomized control trials to identify treatment modalities for radiotherapy induced trismus. Rehabilitation exercises have been implemented across all papers involved in this study which indicates the need for analysis and identification of a pharmaceutical intervention.
KEYWORDS: Head and neck cancer, trismus, lockjaw, radiotherapy, randomized controlled trial, placebo
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INTRODUCTION

HNC comprises of malignancies related to the oral cavity and the head and neck area. Cancer of the bones of the craniofacial region, the glands in the head and neck and the structures and epithelium inside the oral cavity are all included within this group of malignancies.[1]

HNC entails a long list of comorbidities, and as it stands, HNCs have a potential to be fatal, with a 5-year survival rate post diagnosis for 50% of patients. According to an update by the World Health Organization in 2018, oral cancer was recognized as the 10th most frequently occurring cancer in the world and ranks 7th at cancer induced mortality.[2]

As a standard, radiotherapy remains the first line treatment in the management of HNCs. The total dosage given to patients can be in the range of 50-70 Grays (Gy) overall with a daily fraction of 2 Gy over several weeks to effectively eliminate tumour cells while minimizing side effects to surrounding soft tissues.[3]

Radiotherapy can have multiple side effects to the head and neck region considering that a lot of important structures are present in the area (nerves, glands, muscles, etc.).[4] These side effects (acute or late/delayed) include, but may not be limited to[5]:

- Osteoradionecrosis
- Salivary gland hypofunction (Xerostomia)
- Dental Caries
- Thyroid gland hypofunction
- Oral mucositis
- Neuropathic pain
- Radiation Induced Muscle Fibrosis:

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o Trismus
o Dysphagia
o Dysgeusia

Side effects of the therapy/interventions leave patients with, in most cases, a permanent morbidity.

This is due to the effect of given therapies/interventions, which may target important structures in the head and neck region (salivary glands, muscles, etc.) and cause irreversible damage. Patients may feel difficulty in speaking, swallowing, opening their mouths, stretching/turning their neck among other things. Trismus is a condition characterized by limited mouth opening; it may result from the growth of a tumour into the temporomandibular joint (TMJ) or into the muscles of mastication.[6] The complete aetiology of trismus is discussed later under a separate sub-heading.

Trismus as a side effect is resultant limited mouth/jaw opening and mobility, leading to a reduction in patient quality of life (QOL).[7] Currently, there is no clear consensus in the definition of trismus, but most authors suggest the cut-off measurement for trismus to be less than or equal to 35mm interincisal distance.[8,9]

Complications of trismus present as an inability to open the mouth widely. As a result, oral hygiene may be impaired, there is difficulty in patients trying to chew or eat, rehabilitation of teeth presents to be a challenge. There may also be concomitant dry mouth which in turn leads to impaired speech and difficulty in wearing dentures. Patients are at an increased risk of dental infections.[10]

The point of this review was to establish:

- Are there any effective therapies?
- Are there any trials which have confirmed effective therapies?
- Is there a knowledge gap in this area?

The purpose of this review was to systematically assess the outcome of interventions used to treat patients who have trismus as a result of radiotherapy to the head and neck region in the treatment of HNC.

METHODOLOGY

Literature Search

Two researchers (M.A.A & O.B) entered search terms on 3 separate online databases. The following electronic online databases were searched after developing an inclusion and exclusion criteria, complying with the preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[11]:

- Embase (Ovid) – 1980 to present
- Medline (Ovid) – 1946 to present
- Cochrane Library (central)

Search strategies with filters for RCTs were identified and the searches were carried out on the following dates:

- Embase: 19th of June 2019 and 5th of August 2020 with the OVID ISSG filter - InterTASC
- Medline: 19th of June 2019 and 5th of August 2020 with the Cochrane Filter (Cochrane Highly Sensitive Search Strategy – HSSS)
- Cochrane Library: 19th of June 2019 and 5th of August 2020

Inclusion Criteria:

- Randomized and non-randomized controlled trials were reviewed
- Trials aimed at treatment of radiotherapy induced trismus specifically

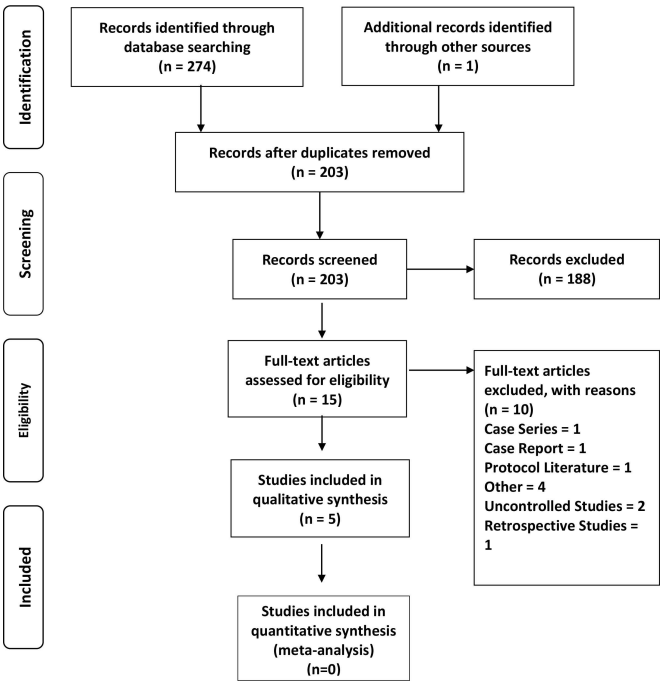
Exclusion Criteria:

- Animal studies were not considered.
- Articles reporting patients with accidental exposure to radiations were not considered
- Preventative measures before or during radiotherapy to prevent trismus were excluded
- All retrospective studies were dismissed

Data Collection and Analysis

Cochrane Collaboration tool for assessing the risk of bias was used to evaluate the quality of articles.[12] This tool has been cited multiple times in many studies which shows the validity of the tool in assessing the risk of

Table 1: PRISMA 2009 Flow Diagram



bias.[13,14] The articles included have been published in various medical and dental journals and no articles are incomplete or in press.

RESULTS

We identified 5 studies which were targeted towards the treatment of RT induced Trismus. Trials using preventative measures before or during treatment were not considered.

A total of 5 trials (Table 2) were identified to have directly dealt with the treatment of RIF, incorporating a total of 365 patients. All trials used the difference in measurement of MIO before and after treatment to determine the success/failure of the trial (through measurement tools such as a ruler). Patient Questionnaires were also used to assess patient-based feedback. Patient questionnaires used for these studies included the Gothenburg Trismus Questionnaire (GTQ)[15-17] , European Organization for Research and Treatment of Cancer Core Questionnaire (EORTC QLQ-C30) (15-18) and the EORTC Head & Neck Questionnaire (EORTC QLQ-H&N35).[16]

These studies assess MIO before and after treatment, with the following timelines:

1. At the start, at 4 weeks then at 10 weeks after intervention with a follow up of 3 months.[16]
2. At the start and 8 weeks after intervention with a follow up of 24 months.[15]
3. At the start and 3 months after intervention.[17]
4. At the start, at 3 months and at 6 months after intervention.[18]
5. At the start, then at every month for 3 months.[19]

Table 2:

Authors	Year	Study Title	Study Design
Lee	2018	Randomised feasibility study to compare the use of Therabite®® with wooden spatulas to relieve and prevent trismus in patients with cancer of the head and neck[12]	Prospective Randomized Study with 2 Intervention Groups
Pauli	2015	Treating trismus: A prospective study on effect and compliance to jaw exercise therapy in head and neck cancer [9]	Prospective Randomized Study with 2 Intervention Groups
Pauli	2016	Exercise intervention for the treatment of trismus in head and neck cancer - a prospective two-year follow-up study[10]	Prospective Non-Randomized Controlled Study
Pauli	2014	Exercise intervention for the treatment of trismus in head and neck cancer [11]	Prospective Non-Randomized Controlled Study
Tang	2010	A Randomized Prospective Study of Rehabilitation Therapy in the Treatment of Radiation-induced Dysphagia and Trismus(1[3])	Prospective Randomized Study with 2 Intervention Groups

An open-label trial assessed the efficacy of a 10-week structured exercise program with exercise five times a day with Therabite® or Engstrom jaw mobilizing device versus no intervention. Participants (n=101) were invited to be part of the study if they had trismus (MIO<35mm) and had completed radiotherapy by at least 3 months. The primary endpoint in this study was MIO and secondary endpoints were trismus-related symptoms (assessed through Gothenburg Trismus Questionnaire) and QoL (EORTC QLQ C30 including the H&N35 module and Hospital Anxiety and Depression Scale). The results of this study were not reported for single interventions (Therabite® or Engstrom device) but at 3 months the authors reported a statistically significant difference of 6.4mm (intervention) vs 0.7mm (control) when the maximal interincisal opening was compared to the baseline. There was a statistically significant difference in trismus-related symptoms and quality of life for the intervention vs control group. The study was considered at high risk of detection and performance bias.

The following year Pauli's research group also published a randomised trial comparing two different jaw exercise devices. The authors included 50 patients and randomly allocated them to 2 groups of 25, one to undergo exercises with the Therabite® device (mean use was 2.5 months) and one to undergo therapy with the Engstrom device (mean use was 2.7 months). The trial proved successful, with the maximum change noticed after 4 weeks of jaw exercises. 10-week exercises were carried out with MIO measurements at 4 weeks, 10 weeks and at a 3 month follow up appointment. The GTQ was used to assess patient feedback and response.[7] patients, 4 from the Therabite® group and 3 from the Engstrom group reported to have used the exercise sporadically due to a variety of reasons (depression, soft tissue necrosis, could not stand the taste of wood, uncomfortable sensation and others). For both groups, MIO increased at 7.2mm for the Therabite® group and 5.5mm for the Engstrom group. At the end of the trial, 21 patients from the Therabite® group and 15 patients from the Engstrom group were reported to not fulfilling the criteria for trismus. The authors reported on patient feedback through the GTQ and exercise diaries were kept for record to reflect on patient compliance to the exercises themselves. No adverse effects were recorded for any of the exercise using both different systems. Allocation bias was not present; patients were randomly selected to have therapy targeted by either one device or the other.[15] The study was considered at high risk of performance bias.

In 2016 Pauli et al. included 50 patients with a history of HNC treatment and trismus to compare with a control group of another 50 participants (31 men and 19 women in both groups). The control group was comparable to the intervention group in terms of age, tumour location, radiation dose and comorbidity. This non-randomized study reported a higher MIO at the 2 year follow up mark of 40.5mm in the intervention group compared to a

34.3mm MIO in the control group. Patient based assessment was made through the GTQ, QLQ-H&N35 and the QLQ-C30 questionnaires. The study reported a positive outcome with the use of the structured jaw exercises with the Therabite® and the Engstrom devices, this time made significant by the comparison of the intervention and the control groups. However, it was not reported how many patients were using the Therabite® device and how many were using the Engstrom devices. Overall, there were no side effects reported. After a 2 year follow up out of the 50 patients in the intervention group, 6 were lost to follow up, 2 died 4 were lost to unspecified reasons. Of the 50 patients in the control group, 7 were lost to follow up, 6 died and 1 was lost to an unspecified reason. The authors reported a positive outcome of using jaw exercises to treat trismus, along with better QOL and better trismus related symptoms (16). This study is at the risk of selection (randomization), performance and detection bias.

In 2010, Tang et al. conducted a randomized prospective study with 43 patients who had undergone radiotherapy for nasopharyngeal carcinoma. Trismus was evaluated through the LENT/SOMA score as well as measuring the MIO. Quality of life was not assessed through any questionnaire. Two groups were made with 21 patients in the control group versus 22 in the rehabilitation group. The rehabilitation group was asked to conduct jaw exercises by:

1. Opening and closing the mouth
2. Opening the mouth slightly and inducing lateral movements in the mandible
3. Stretching the chin downwards
4. Using the Therabite® device

MIO was measured at the start of the trial and then once a month for 3 months. The rehabilitation group showed a lesser decrease in MIO (Pre-treatment = 1.89+/-0.69cm vs. 3-month post-treatment=1.7+/-0.68cm) as compared to the control group (Pre-treatment = 1.8+/-0.56cm vs. 3-month post-treatment=1.1+/-0.36cm). The results were statistically significant. This study, however, does not clarify the details of the two groups formed for this trial and hence is at the risk of allocation and detection bias.

In 2018 Lee et al. assessed the efficacy of the Therabite® device versus wooden spatulas in a total of 71 patients with n=37 and n=34 respectively. QOL was measured by the use of EORTC QLQ-C 30 and the Head and Neck module (EORDC QLQ H&N 35). Baseline values for MIO in the Therabite® group was at a mean of 24 mm and 21.8 mm for the spatula group. This trial found that the difference between the two groups in terms of increased MIO was not statistically significant. A comparison was not made with other subjects due to the absence of a control group. A few patients were lost because of non-compliance. This trial did not include a control group hence a comparison could not be made with regards to proving which device served better against participants who were not receiving any treatment. This study is at the risk of performance bias.

The results have been summarized in Table 3 below: [Table 3]

Table 3:

Authors	Number of Participants	Study Design	Intervention	Outcome (MIO change)	Trismus Symptoms	QoL	Risk of Bias
Pauli et al., 2014	50 intervention + 50 control	Prospective Non-Randomized Controlled Study	Therabite® and Engstrom devices	MIO increase of 6.4 mm (intervention) vs 0.7mm (control)	Reported as diminished in the intervention group	GTQ, QLQ-H&N35 and the QLQ-C30 questionnaires were used to report patient QoL	High risk of detection and performance bias
Pauli et al., 2015	50	Prospective Randomized Study with 2 Intervention Groups	Therabite® and Engstrom devices	7.2mm increase in Therabite® group 5.5mm increase in Engstrom group	Reported as diminished in 36 patients	Reported through the GTQ and exercise diaries filled by the patients	High risk of performance bias
Pauli et al., 2016	51 Intervention + 50 Control	Prospective Non-Randomized Controlled Study	Therabite® and Engstrom devices	MIO increased; maximum increase was at the 4-week mark (increase to 40.5mm)	Reported as diminished in the intervention group	GTQ, QLQ-H&N35 and the QLQ-C30 questionnaires were used to report patient QoL	High risk of selection (randomization), performance and detection bias
Lee et al., 2018	37 Therabite® + 34 Wooden Spatula	Prospective Randomized Study with 2 Intervention Groups	Therabite® device and wooden spatulas	MIO not measured due to patient fallout	N/A	EORTC QLQ-C 30 and EORTC QLQ H&N 35 questionnaires were used	High risk of performance bias
Tang et al., 2010	22 in control group + 21 in rehabilitation group	Prospective Randomized Study with a control group and an intervention group	Jaw exercises and Therabite® device	MIO reduction was minimum at the three-month mark with intervention	N/A due to unavailability of QOL questionnaires	N/A	High risk of allocation and detection bias

MIO - Maximum Interincisal Opening
GTQ - Gothenburg Trismus Questionnaire
H&N35 - European Organization for Research and Treatment of Cancer Head and Neck Questionnaire
QLQ-C30 - European Organization for Research and Treatment of Cancer Core Questionnaire

DISCUSSION

Head and Neck Cancer (HNC) related side effects have been long documented. Trismus is one of the most debilitating side effects associated with the treatment of HNC, but there is a distinct lack of the interventions to ameliorate trismus, thus the need arises for us to find a good treatment(s) option. This systematic review was carried out keeping in mind the absence of HNC radiotherapy induced trismus related interventions.

We included 5 studies in this systematic review with a total of 365 participants. All 5 studies used exercise-based interventions. The above studies, although reporting on patient outcomes of intervention, lack strong evidence provided by Randomized Controlled Trials.

A clinical trial is planned by the University College

London and the National Institute for Health Research in the United Kingdom to study the effects of Pentoxifylline and Tocopherol in the management of RT induced trismus (due to end in late 2021). This trial will be one of the first Randomized Controlled Trials to research the effect of the above stated drugs in the management of RT induced trismus, and will provide solid, robust evidence in comparison to the rest of the available literature. The results of this trial will help in determining whether the use of Pentoxifylline is justified in patients with RT induced trismus.

Chua et al. selected a total of 16 patients (12 men and 4 women) to undergo an 8-week course of Pentoxifylline 400mg, 3 times a day. During this course, 4 patients developed side effects and were given the same dose only twice daily until the end of the timeline. The mean MIO before the experiment was 12.5 mm and the trial reported an increase to a mean of 16.5 MIO at the end for all patients. 10 patients were reported to have a range increase of 2-25 mm of MIO, 5 patients were reported to have no measurable change and 1 patient had a reduced MIO after therapy.

The authors did not report patient feedback regarding the trial or the effect of outcome experience by the patients. The reported adverse effect was dizziness, reported in 4 patients which warranted a dose reduction in these patients.[20] This trial was excluded as it had no control group.

Hartl et al. selected a total of 19 patients (12 men and 7 women) to undergo therapy with Botox injections (50 units) or Dysport injections (250 units). These transcutaneous injections were given to the masseter muscle.

The author reported no significant change in the MIO before and after injections were given up to a period of 1 month. The author did however report that after the injections were made, patients reported betterment of the functional pain and cramps associated with their conditions, but no improvement was mentioned for trismus. Patient feedback was taken through a questionnaire which was designed for the trial but not been used anywhere else in the literature.

However, all patients were reported to have an improvement in the aspect of their pain and it was reported that they would recommend the treatment to others experiencing the same symptoms, even though the therapy had no effect on the trismus. Seven patients described the injections as 'painful'.

The authors did not evaluate the symptoms of trismus. No adverse side effects were reported for this trial.[21] This trial was excluded as it had no control group.

CONCLUSION

1. Trials are warranted as there is a need to manage RT induced trismus to improve trismus related symptoms as well as to improve patient QOL. Further research is needed to assess the best treatment intervention for HNC patients with established radiotherapy induced trismus.

2. Preliminary reports suggest the efficacy of structured jaw exercises or rehabilitation exercises as a treatment for trismus however there is limitation due to the absence of randomized controlled trials.

3. Proper RCTs with a low risk of bias, proper blinding techniques and a large sample size will help develop robust evidence to find interventions which are useful in the management of RT induced trismus.

CONFLICT OF INTEREST

None declared

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