Trismus in head and neck cancer patients

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DOI:
10.33612/diss.112040321

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General discussion

The general aims of this thesis were to determine the criterion for trismus, to identify factors associated with trismus and to assess the effectiveness of stretching regimens as therapy for trismus, in head and neck cancer patients.

Criterion for trismus

In chapter 2, a maximal mouth opening (MMO) of 35 mm or less was confirmed as the cut-off point for trismus in a large database of head and neck cancer patients (n=671). Patients' perception of difficulties opening the mouth are more likely to increase if their MMO is below this cut-off point. The difficulties of opening the mouth are often accompanied by difficulties with chewing, diet, oral hygiene and mandibular function.[1,2] Consequently, these difficulties, will most likely affect the general quality of life.[2]

The cut-off point of 35 mm or less, which is in line with previous studies,[1,2] can be used to monitor patients after cancer treatment, to build prediction tools for trismus, and to evaluate a therapy for trismus.

Factors associated with trismus

Chapters 3a, 3b, 4, and 5, identified the factors associated with trismus or a decrease in mouth opening. The baseline MMO is one of the factors influencing trismus (chapter 4 and 5). A smaller MMO at baseline increases the risk of trismus after treatment.[3,4] One study found that if the baseline MMO is smaller than 40.5 mm, there is a significantly higher chance of developing trismus after treatment compared to when it is greater than 40.5 mm (Odds Ratio (OR) 5.44; 95% Confidence Interval (CI) 1.42;20.85, p=0.013).[5] Another study found that a baseline MMO of 46 mm or less results in a significantly higher risk of developing trismus after treatment.[6] In chapter 4, the influence of the baseline MMO was assessed more precisely, by building a multivariate logistic regression model. This model showed that with every millimetre increase in the baseline MMO decreases the risk of developing trismus (β= -0.09, OR 0.91, 95% CI 0.89; 0.93, p<0.001).

The risk of trismus differs per tumour localization (chapters 3a, 3b, and 4) and per treatment modality (chapter 3a and 3b). Regarding tumour localization, trismus will most likely occur when the masticatory muscles (such as the medial pterygoid muscle[6], the lateral pterygoid muscle[7] and the masseter muscle.[6-8]) are affected.

In chapters 3a, 3b, and 4, we found that tumours in the close proximity of these muscles, such as the maxilla, mandible, cheek, major salivary glands, oropharynx, and nasopharynx increase the risk of trismus. Regarding treatment modalities, trismus is more likely to develop after (chemo) radiotherapy than after surgery (chapter 3a and 3b).

A partial recovery was seen six months after surgery.[4,9] This recovery was not seen after (chemo) radiotherapy, with a persisting decreased in MMO over time.

Therapy for trismus

In chapter 6, the effects of stretching exercises on trismus were studied. The high attrition and low compliance, a common phenomenon in similar trials of head and neck cancer patients, made it difficult to study the effects of the stretching exercises. The most frequently reported reasons for attrition were: problems with the application of the stretching device, the feeling that the stretching protocol was too intensive, and additional pain in the head and neck area.

The problems with applying the stretching devices (such as limited access to the mouth) are also described in chapter 6. Another study described problems with application of the devices as well (such as the discrepancy between the position of the biting plates of the TheraBite® Jaw Motion Rehabilitation System™ and a large dental horizontal overbite).[10] To lower the attrition rates and to improve the compliance, it might be worthwhile to consider other forms of stretching which could be chosen according to what is most comfortable for the patient.

Recovering from the cancer treatment itself, managing all the side- effects, and receiving an intensive burdensome therapy for only one of these side-effects (trismus), all at once, is a lot to cope with. The intensity and burden of the therapy (in terms of timing, duration, frequency, force, and accompanied intense pain) should be balanced out with the effect of the therapy. In a systematic review, no conclusions could be drawn regarding as to which timing, duration, frequency, and force of the therapy is best, due to the clinical and methodological heterogeneity of the studies.[11] More research into these aspects is necessary.

In a qualitative study, the patients performing stretching exercises using the TheraBite® Jaw Motion Rehabilitation System™ were interviewed regarding factors influencing their compliance. Perceptions of no effect, reaching the exercise goal or a plateau in mouth

opening, or limitations of the stretching device negatively influenced compliance.[12] Reaching a plateau of perceiving no effect could have been attributed to the extensibility capacity of the tissue. A study found that scar tissue is not able to extend as far as healthy tissue.[13] Additionally, scar tissue cannot be extended during stretching beyond a certain intrinsic extensibility. This intrinsic extensibility is dependent on the individual patient and the extensiveness of the scar tissue. Increasing the stretching force will not lead to further improvement, but could damage the tissue unnecessarily.[13]

The difference in the extensibility of healthy versus scar tissue may suggest that the stretching exercises should be started before scar tissue has formed and the extensibility has been limited. To analyse the effects of early, or even preventive stretching on trismus, is difficult, because it is difficult to select only the patients at risk for trismus[14] and because mouth opening changes over time independent of the stretch.[15] However, chapters 3a, 3b, 4 and 5 identify factors associated with trismus, making it easier to select the patients at risk of trismus. The changes of maximal mouth opening after oncological treatment are displayed in Figure 2B of chapter 6. Mouth opening may increase after cancer treatment as part of the recovery after surgery[4, 9] or as part of the recovery from mucositis after radiotherapy[15], and not necessarily due to the stretching exercises. As stated earlier, no clear conclusion can be drawn as to what is the best time to initiate the therapy.[11]

Besides trying to improve compliance by modifying aspects of the therapy, attempts at providing a support system for patients have been studied as well. A smartphone medical app with information and instruction for the patients resulted in better compliance (partial or full compliance by the intervention group was 61%, versus 43% by the control group, χ^2=7.37, p=0.013) and also less mouth opening difficulties 6 months after the cancer treatment (67% of the intervention group had no mouth opening difficulties versus 35% of the control group, χ^2=-2.40, p=0.017).[16] A remote support system via the telephone resulted into a better compliance (intervention group 93%, versus control group 17%), more practice time per week (intervention group 303.3 , SD 204.0 minutes versus control group 3.7, SD 7.8 minutes) and a greater MMO (intervention group 27.3 (9.7) millimetres versus control group 16.2 (8.0) millimetres).[17] Such initiatives encourage the patients to comply during the intensive and burdensome therapy.

Strengths & limitations

The strength of this thesis, is that chapters 2, 3a, 3b and 4 are based on large sample sizes. These large sample sizes gave us the opportunity to perform multivariate and covariate analyses. Due to large sample sizes and the broad variety of head and neck cancer histologies, locations and treatments, our results can be generalized for head and neck cancer patients.

A limitation of our study is that the MMO was measured on unstructured time points, regarding chapters 2,3a and 3b. It was not possible to correct for or to exclude the influence of time. Future research should study fixed time points.

Another limitation is the high attrition, especially in the randomized controlled trial (chapter 6). Relatively high study attrition is expected in cancer research, due to death or tumour recurrence. Thus, analyses were sometimes not possible (for example analysing the time point 48 months after radiotherapy in chapter 4 or further analyses in chapter 6) or it was necessary to impute data (missing data in chapter 4).

Clinical, scientific and future perspectives

The same cut-off point of a MMO of 35mm or less for trismus was used in a systematic review and meta-analysis to determine the prevalence of trismus. The prevalence of trismus was on average 17% (95% CI, 11%; 27%) before treatment and went up to 33% (95% CI, 22%-45%) 3-10 years after treatment, with the highest prevalence being 44 % (95% CI, 37%-52%) six months after treatment.[18] Since trismus has been reported as one of the most burdensome side-effects after head and neck cancer treatment and it impairs patient' quality of life in general, there is a need to reduce this high prevalence of trismus.[19-21]

The identified factors associated with trismus (chapters 3a, 3b, 4 and 5) can be used as a basis to reduce their effects on trismus. Attempts have already been made to improve cancer treatment modalities. For example, advances have been made in reconstructive surgery. Three-dimensional digital planning and individualized manufactured constructions might add to a better end-point for subsequent oral rehabilitation and thereby may improve overall well-being, cosmetic and functional results.[22,23] Furthermore, conventional radiotherapy is gradually being replaced by intensity-modulated radiotherapy (IMRT), proton therapy, or carbon-ion therapy. The more specific modulation of the intensity of the radiation beams and the better in-depth dose distribution means the tumour is being treated whilst the doses to the surrounding tissues (risk structures)

are reduced, thereby reducing the chance of developing side-effects, such as trismus.[24-26] Despite all the attempts to reduce the risk of trismus, trismus is sometimes unavoidable after head and neck cancer treatment. Therefore, therapy to prevent or treat trismus still needs to be optimized as well.

Besides optimizing aspects of stretching exercise therapy, it might be useful to look for alternative therapy options as well. Scar formation, or fibrosis, is the underlying cause of trismus development. Hence, more strategies should be devised to limit or prevent this fibrosis. Improving the tissue condition might be one of those options. Improving the condition of the tissue through the use of pentoxifylline, showed a minor effect on mouth opening (mean increase 4mm, 95% CI 0.6; 7.4, n=16).[27] Low intensity ultrasound or low level laser therapy may be promising therapies to increase mouth opening. [28,29]

When the tissue is in a better condition, it might be more extensible. If an (optimized) stretching exercise therapy is then added in order to extent the tissue, more increase in mouth opening is expected. Applying low intensity ultrasound or low level laser therapy in combination with an exercise therapy led to an additional increase of approximately 10 mm in MMO. [29] However, the effectiveness of low intensity and ultrasound or low level laser therapy still needs to be evaluated in future high quality randomized controlled trials.

Conclusion

Patients treated for head and neck cancer experience functional difficulties in opening their mouth most likely when having a MMO of 35mm or less. A small baseline mouth opening, tumours located in the close proximity of the masticatory muscles, and extensive cancer treatment contribute most to the development of trismus. In order to treat or prevent trismus, therapy for trismus needs to be optimized.

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