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FISIOTERAPIA PROFILÁTICA AO DESENVOLVIMENTO DO TRISMO RADIOINDUZIDO EM PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO

PORTO ALEGRE
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Dissertação de Mestrado apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Fundação Universidade Federal de Ciências da Saúde de Porto Alegre, como requisito parcial para a obtenção do título de Mestre em Ciências da Saúde.

Orientador: Prof. Dr. Geraldo Pereira Jotz
Co-orientador: Prof. Dr. Marcelo Faria Silva

PORTO ALEGRE
2015

Dedico este trabalho...

...àqueles que muitas vezes adiaram seus sonhos em prol dos meus...

Mãe, Pai, Gio, esta vitória é nossa!

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"QUE DEUS ME DÊ A SERENIDADE PARA ACEITAR AS COISAS QUE NÃO POSSO MUDAR, CORAGEM PARA MUDAR AS QUE POSSO, E SABEDORIA PARA DISTINGUIR ENTRE ELAS."

(ABRAHAN LINCOLN)

RESUMO

Introdução: O trismo radioinduzido é definido como uma hipomobilidade mandibular decorrente do tratamento radioterápico na região da cabeça e pescoço. Devido ao trismo radioinduzido ter um impacto negativo na qualidade de vida dos pacientes com câncer de cabeça e pescoço, a fisioterapia torna-se um recurso essencial tanto para prevenção quanto para tratamento desta comorbidade, porém, ainda não existe consenso sobre qual o melhor regime fisioterapêutico a ser empregado na prevenção do trismo radioinduzido. Objetivos: Verificar o efeito de dois protocolos de exercícios fisioterapêuticos na manutenção da amplitude de movimento mandibular dos pacientes com câncer de cabeça e pescoço em tratamento radioterápico e secundariamente associar a variável abertura bucal às variáveis demográficas, clínicas e adesão ao protocolo de exercícios. Métodos: Este estudo trata-se de um ensaio clínico randomizado paralelo controlado. Noventa pacientes foram randomizados em três grupos: Grupo exercícios TheraBite-Hiperbolóide (GETH), Grupo exercício Hiperbolóide (GEH) e Grupo controle (GC). A mensuração da mobilidade mandibular, através de paquímetro, foi realizada antes e após a radioterapia. Resultados: Houve uma tendência de redução da abertura bucal (AB) em todos os grupos, sendo essa redução menor no GETH, porém sem significância estatística (p=0,246). Na avaliação intra-grupo a redução de AB foi estatisticamente significativa no GC (p=0,015). Quando analisada a AB em relação à adesão ao protocolo, observou-se que o GETH apresentou um aumento de AB nos pacientes que adeririam ao tratamento e nos que não adeririam houve uma redução da AB, sendo essa diferença estatisticamente significativa (p=0,007). No GEH os pacientes que aderiram ao protocolo reduziram menos a AB quando comparado aos que não aderiram, porém sem significância estatística (p=0,295). Após análise de covariância permaneceram associadas com a variação da AB as variáveis: grupo (p=0,022) e variação do grau de mucosite (p=0,027). O GETH apresenta uma variação menor da AB (0,50 ± 1,28) do que o GC (-3,78 ± 1,25). O GEH não apresentou diferença significativa para nenhum dos dois grupos (-2,10 ± 1,50). A mucosite é um fator independente associado com a redução da AB. Conclusão: Concluí-se que um protocolo de reabilitação associando o TheraBite com treino de mastigação com o hiperbolóide é o mais adequado para manutenção da medida de AB durante a radioterapia, devendo-se controlar a adesão desses pacientes ao tratamento e, sugerindo, que protocolos de profilaxia à mucosite sejam investigados.

Palavras-chave: Neoplasias de cabeça e pescoço. Trismo. Amplitude de movimento articular. A. Modalidades de fisioterapia. Terapia por exercício.

ABSTRACT

Introduction: Radiation-induced trismus is defined as a mandibular hypomobility resulting from radiotherapy treatment in the head and neck area. Because radiation-induced trismus has a detrimental effect on the quality of life of patients with head and neck cancer, physiotherapy has become an essential resource in treating and preventing the disease. However, there has been no agreement so far on the best physiotherapy regime to be adopted in the prevention of radiation-induced trismus. ObjectiveS: To observe the effect of two protocols of physiotherapy exercises adopted in order to maintain mandibular range of movement in patients with head and neck cancer who are receiving radiotherapy treatment. Also, to compare the mouth opening variable to other variables, such as demographics, clinical and exercise compliance. Methodology: This was a randomized, controlled, parallel-group clinical trial. Ninety patients were randomized in three groups: Exercise group with TheraBite-Hyperboloid (THEG) , Exercise group with Hyperboloid (HEG) and Control group (CG). The measurement of mandibular mobility, with the use of a pachymeter, was carried out before and after radiotherapy. Results: A tendency towards decreased mouth opening (MO) in all groups was found, this was smaller in THEG, however without statistic significance (p=0,246). In the intra-group assessment the decrease in MO was statistically relevant in CG (p=0,015). When MO was analysed in relation to protocol compliance, in THEG there was an increase in MO in patients who complied with the treatment. In those who did not comply, there was a decrease in MO which was statistically significant (p=0,007). In HEG, the patients who complied with the protocol had a smaller decrease in MO when compared to those who did not comply, however without statistical significance (p=0,295). After analysing the covariance the following variables continued to have na association with the MO variable: group (p=0,022) and degree of mucositis (p=0,027). THEG presented a smaller variation of MO (0,50 ± 1,28) than CG (-3,78 ± 1,25). HEG did not show any significant variation in relation to any of the other groups (-2,10 ± 1,50). Mucositis is an independent factor associated with the reduction in MO. Conclusion: a rehabilitation protocol including the use of TheraBite combined with mastication training was found to be the most adequate treatment for keeping the MO measurement during radiotherapy. Patient compliance to treatment should be monitored and there is a need further research on a prophylactic protocol for mucositis.

Keywords: head and neck neoplasms. Trismus. Joint range of motion. Radiotherapy. Physical therapy. Exercise therapy.

LISTA DE ILUSTRAÇÕES

LISTA DE SIGLAS E ABREVIATURAS

5-FU	5-Fluorouracil
AB	Abertura bucal
ADM	Amplitude de movimento
ATM	Articulação temporomandibular
CCP	Câncer de cabeça e pescoço
CEC	Carcinoma espinocelular
cGy	*Centigray*
CG	*Control Group*
DNA	*Deoxyribonucleic acid* - Ácido desoxirribonucleico
GC	Grupo controle
GEH	Grupo exercício Hiperbolóide
GETH	Grupo exercício TheraBite-Hiperbolóide
Gy	*Gray*
HEG	*Hiperbolóide exercise group*
HPV	*Human Papillomavirus* - Papiloma vírus humano
IMRT	*Intensitiy Modulated Radiation Therapy* - Radioterapia de intensidade modulada
INCA	Instituto Nacional do Câncer
KPS	*Karnofsky Perfomance Status*
MO	*Mouth opening*
OTG	Órgão tendinoso de *Golgi*
QV	Qualidade de vida
Rad	*Radiation Absorved Dose*

RT	Radioterapia
RT2D	Radioterapia convencional bidimensional
RT3D	Radioterapia tridimensional conformada
THEG	*TheraBite-Hiperboloide exercise group*
UW-QOL	*University of Washington Quality of Life Questionnaire*

SUMÁRIO

1 INTRODUÇÃO

1.1 CÂNCER DE CABEÇA E PESCOÇO

O câncer de cabeça e pescoço (CCP), segundo SHERMAN (1996), abrange um grupo heterogêneo de neoplasias agrupadas devido a sua relação anatômica. Os sítios anatômicos que constituem esse conjunto de neoplasias abrangem: a cavidade oral (mucosa bucal, lábios, gengivas, palato duro, 2/3 anteriores da língua, assoalho da boca e trígono retromolar); faringe, sendo essa subdividida em orofaringe (base da língua, valécula, palato mole, úvula e lojas amigdalianas), nasofaringe e hipofaringe (seios piriformes e área pós-cricóide); cavidade nasal e seios paranasais; laringe, sendo essa subdividida em regiões glótica, subglótica e supraglótica; e glândulas salivares (ALVARENGA et al. 2008; COLOMBO e RAHAL 2009).

Excluindo-se os cânceres de pele, o CCP representa, mundialmente, 10% dos tumores malignos, onde 40% dos casos acometem a cavidade oral, 25% a laringe, 15% a faringe, 7% as glândulas salivares e 13% os demais locais (CARDOSO et al. 2005; DOBROSSY 2005). O Instituto Nacional do Câncer – INCA – estima que ocorrerão no Brasil, em 2014, 576 mil novos casos de câncer. Desses, estima-se 11.280 novos casos de câncer em cavidade oral entre os homens e 4.010 entre as mulheres (Ministério da Saúde 2014).

Vários fatores estão envolvidos na gênese dos tumores de cabeça e pescoço, incluindo predisposição genética (CHOI e MYERS 2008; COLOMBO e RAHAL 2009; BABRON et al. 2014), infecção pelo papiloma vírus humano – HPV (RAMPIAS et al. 2014), condições e hábitos sociais, sendo o consumo de tabaco e bebidas alcoólicas os fatores de risco mais significativos para o desenvolvimento dessas neoplasias (FRANCO et al. 1989; CACCELLI e RAPOPORT 2008; CONWAY et al. 2008; COLOMBO e RAHAL 2009). Variáveis como idade acima de 40 anos, sexo masculino e raça branca também podem ser considerados como fatores predisponentes ao seu desenvolvimento (ALVARENGA et al. 2008).

A grande maioria dos tumores malignos de cabeça e pescoço é de origem epitelial, sendo 90% carcinomas de células escamosas (WARNAKULASURIYA 2009). Outras histologias incluem linfomas, carcinomas cístico-adenóides, e com menor freqüência, sarcomas e melanomas. Os adenocarcinomas são menos comuns, porém, a maioria se origina nas glândulas salivares, fossa nasal e seio maxilar (SHERMAN 1996).

As modalidades terapêuticas para tratamento dos tumores malignos de cabeça e pescoço incluem procedimentos cirúrgicos, radioterápicos e quimioterápicos que podem ser utilizados isoladamente ou em conjunto (RIDDER 1993; JHAM e FREIRE 2006; CACCELLI

e RAPOPORT 2008). O regime terapêutico escolhido é baseado no local anatômico, histologia, estadiamento tumoral e condições clínicas do paciente (VISSINK et al. 2003b). A cirurgia e a radioterapia (RT) são os principais e mais eficazes métodos de tratamento do CCP, consistindo em formas de tratamento para doença localizada ou com disseminação regional (CARDOSO et al. 2005; JHAM e FREIRE 2006).

1.2 TRATAMENTO RADIOTERÁPICO

A RT é uma modalidade de tratamento dos tumores malignos cujo agente terapêutico é a radiação ionizante, ou seja, aquela que promove ionização no meio onde incide tornando-o eletricamente instável (JHAM e FREIRE 2006; ROCHA et al. 2008). Ao criarem-se átomos instáveis, cujos elétrons livres se unem a outros átomos adjacentes, que também se tornam instáveis com cargas negativas aumentadas, danifica-se o ácido desoxirribonucléico (DNA) celular impedindo a replicação da célula neoplásica (SALAZAR et al. 2008).

Como o conteúdo de DNA duplica durante a mitose, as células com alto grau de atividade mitótica são mais radiossensíveis em relação àquelas com baixa taxa de mitose. Sendo assim, por estarem em constante processo de multiplicação, as células neoplásicas são passíveis de sofrerem os efeitos da radiação (JHAM e FREIRE 2006). Entretanto, a capacidade de multiplicação varia de acordo com o tipo celular, existindo uma escala de radiossensibilidade tanto para as células tumorais quanto para as células normais (ROCHA et al. 2008). O tratamento ionizante, contudo, não é seletivo, pois não possui a capacidade de diferenciar as células normais das células malignas, o que o torna tóxico para o organismo (SALAZAR et al. 2008).

As radiações ionizantes são divididas em corpusculares e eletromagnéticas. As radiações corpusculares são representadas pelos elétrons, prótons e nêutrons. As radiações eletromagnéticas são chamadas de fótons, sendo representadas pelos raios x e pelos raios gama. Na prática clínica, a maior parte dos tratamentos radioterápicos é feita através do uso de fótons (JHAM e FREIRE 2006). De acordo com Rice (1997) citado por SALAZAR et al. (2008, p.63) o tratamento radioterápico pode ser realizado de duas maneiras: a teleradioterapia, representando a modalidade mais comum de tratamento, onde se emprega uma fonte externa colocada à distância do paciente, através de um aparelho emissor de radiação; e a braquiterapia, que utiliza isótopos radioativos em contato direto com o tumor.

A teleradioterapia pode ser realizada com equipamentos de cobaltoterapia e mais atualmente através de aceleradores lineares, onde os planejamentos bidimensionais ou

tridimensionais podem ser empregados, conforme a técnica de irradiação: RT convencional bidimensional (RT2D), RT tridimensional conformada (RT3D) ou RT com intensidade de feixe modulado (IMRT) (GRAFF et al. 2007; ZHANG et al. 2009; MONTEJO et al. 2011).

De acordo com SASSI e MACHADO (2009) a região na qual o tumor é irradiado é conhecida como campo de radiação. O ponto central do tumor receberá a dose pré-estabelecida pelo radioterapeuta e os tecidos adjacentes receberão doses menores de irradiação. Para expressar a quantidade de radiação absorvida pelos tecidos, foi proposta uma unidade internacional, o rad (*radiation absorved dose*), isto é, a diferença entre a radiação aplicada e a que atravessou os tecidos. Na década de 1980, esta unidade foi substituída pelo Gray, definido como 1 joule por quilograma. O Gray é abreviado como Gy, sendo que: 1 Gy = 100 cGy = 100 rad. (JHAM e FREIRE 2006; ROCHA et al. 2008).

A maioria dos pacientes submetidos à RT de cabeça e pescoço recebe uma dose total de 50 a 70 Gy, quando com finalidade curativa. Essas doses são, geralmente, fracionadas em um período de 5 a 7 semanas, uma vez ao dia, 5 dias por semana, com dose diária de aproximadamente 2 Gy, dependendo do tumor e da rotina hospitalar aplicada (VISSINK et al. 2003ª; JHAM e FREIRE 2006; CACCELLI e RAPOPORT 2008; SASSI e MACHADO 2009). Nos tratamentos adjuvantes, 45 Gy são empregados no pré-operatório e 55-60 Gy no pós-operatório (JHAM e FREIRE 2006).

As reações adversas decorrentes do tratamento radioterápico dependem do volume e da área que será irradiada, se a exposição será uni ou bilateral, da dose total, do tipo de radiação e do fracionamento empregado, da idade, das condições clínicas do paciente, dos hábitos sociais como alcoolismo e tabagismo, além dos tratamentos associados (VIER et al. 2005; ROCHA et al. 2008; SALAZAR et al. 2008; SASSI e MACHADO 2009). Muitos dos pacientes que apresentam CCP são submetidos a altas doses de RT em extensos campos de radiação, que incluem a maxila, mandíbula e glândulas salivares, músculos da mastigação e mucosa oral, acarretando em inúmeras reações adversas (JHAM e FREIRE 2006; ROCHA et al. 2008; KUMAR e RASTOJI 2011).

Os efeitos colaterais da RT instituída para tratamento dos pacientes com CCP interferem significativamente na qualidade de vida (QV) desses indivíduos (LAZARUS 2006; MOWRY et al. 2010). Entre os efeitos localizados na região da cabeça e pescoço, pode-se citar: mucosite, dermatite, xerostomia, hipogeusia, osteorradionecrose, fibrose e trismo (CARDOSO et al. 2005; JHAM e FREIRE 2006; SALAZAR et al. 2008; SASSI e MACHADO 2009; KUMAR e RASTOJI 2011).

1.2.1 Quimiorradioterapia

A combinação de agentes quimioterápicos com a radiação tem uma forte justificativa biológica. Além da atividade citotóxica independente, essas drogas sensibilizam as células malignas à ação da RT. As drogas mais importantes no contexto da quimiorradioterapia, tratando-se do CCP, são o 5-fluorouracil (5-FU) e a cisplatina (ADELSTEIN e RODRIGUEZ 2010).

Na modalidade concomitante, o esquema de administração da QT e da RT deve ser bem avaliado, não somente para permitir a máxima radiossensibilização, mas também para diminuir a toxicidade nos tecidos normais tanto quanto possível. Atualmente, os efeitos adversos nos tecidos normais constituem a principal limitação da quimiorradioterapia concomitante (PIGNON et al., 2000).

Atualmente, na terapia de preservação de órgãos, quimioterapia concomitante a RT é freqüentemente utilizada (TEGUH et al., 2008). Pesquisadores (CHANSEN e BHARGAVA, 2009) relatam que o tratamento combinado apresenta maior benefício para o controle tumoral, por outro lado, aumenta a toxicidade ao organismo resultando em excesso de efeitos colaterais. Alguns autores (VISSINK et al., 2003b; TEGUH et al., 2008; JEREMIC et al. 2011) sugerem que a terapia combinada possa aumentar a incidência de hipomobilidade mandibular, embora não haja consenso (KENT et al., 2008; BRAGANTE et al., 2012).

1.3 TRISMO

Trismo, antigamente, era estritamente definido como uma contração tônica, de um ou mais, dos músculos mastigatórios, o que impedia a abertura bucal - AB – (BASMAJIAN 1982). Atualmente, o termo trismo abrange todas as condições de hipomobilidade mandibular (ICHIMURA e TANAKA 1993; COHEN et al. 2005; SHENOY et al. 2007; SHULMAN et al. 2008; TEGUH et al. 2008).

Mobilidade mandibular normal, descrita na literatura, para abertura bucal varia entre 40 a 70 mm, e 8 a 12 mm para as lateralidades (MEZITIS et al., 1989; KHARE et al., 2012). Esses valores variam de acordo com fatores como gênero, idade, peso corpóreo, estatura, condição dentária e presença de sinais e sintomas de disfunção temporomandibular (DHANRAJANI e JONAIDEL 2002; KHARE et al., 2012). Mobilidade mandibular reduzida, ou trismo, quando relacionada ao CCP, pode ocorrer: por infiltração tumoral na musculatura mastigatória, por infiltração da articulação temporomandibular (ATM); por obstrução

mecânica do processo coronóide da mandíbula pelo tumor (VISSINK et al. 2003a; BHRANY et al. 2007; JOHNSON et al. 2010; STUBBLEFIELD et al. 2010); por dor reativa à infiltração ou irritação tumoral em nervos sensitivos no trajeto da boca, faringe ou base do crânio, levando ao trismo reflexo*[1] (ICHIMURA e TANAKA 1993).

Após intervenção cirúrgica em lesões tumorais que envolvem a musculatura mastigatória ou ATM, o trismo pode se desenvolver como resultado de aderências e fibroses na região cicatricial (ICHIMURA e TANAKA 1993; WHITMYER et al. 1997). Em aproximadamente 2% dos pacientes com CCP, o trismo está presente como um sintoma no momento do diagnóstico (JOHNSON et al. 2010), e, embora esse sintoma alivie ou desapareça durante o curso da RT, ele pode reaparecer gradualmente se ocorrer fibrose na musculatura mastigatória (ICHIMURA e TANAKA 1993).

1.3.1 Trismo Radioinduzido

Trismo radioinduzido é decorrente da fibrose na musculatura mastigatória, quando localizada no campo de radiação, causando redução da mobilidade mandibular (DHANRAJANI e JONAIDEL 2002; KENT et al. 2008; TEGUH et al. 2008; JOHNSON et al. 2010). A musculatura mastigatória - masseter, temporal e pterigóideos (SHULMAN et al. 2009) - quando afetada pela irradiação reage inicialmente através de uma proliferação anormal de fibroblastos acentuando a síntese de colágeno que leva a formação de tecido fibroso espesso (OPPENHEIMER et al. 2004; KENT et al. 2008;TEGUH et al. 2008; BENSADOUN et al. 2010).

DIJKSTRA et al. (2006) em estudo transversal padronizaram o ponto de corte funcional para trismo, em pacientes oncológicos de cabeça e pescoço, como sendo uma AB ≤35 mm, independente da condição dentária e do gênero. Entretanto, mesmo após essa padronização, outros estudos adotaram distintos pontos de corte: KENT et al. (2008) consideraram como critério para trismo, em pacientes dentados, uma AB < 35 mm e, em pacientes edêntulos, AB < 40 mm; SHULMAN et al. (2009) relataram em sua série de casos que trismo é uma AB < 40-45 mm indiferente à situação dentária; já RIBAS et al. (2011)

[1] O estímulo das fibras sensórias das estruturas da mastigação pelos patógenos do tumor transmitem informação ao núcleo trigêmeo na ponte e ao cortex sensorial, onde o estímulo é registrado como dor, enviando essa informação para o núcleo motor do nervo trigêmeo que estimula o reflexo tônico dos músculos da mastigação. Como os músculos de fechamento da boca exercem uma força 10 vezes maior que os músculos de abertura, o paciente não consegue abrir a boca quando os músculos da mastigação estão em espasmo tônico (ICHIMURA e TANAKA 1993)

utilizaram em seu estudo para critério de trismo AB < 40 mm. Também não há consenso quanto à forma de avaliação da medida de AB. Esta pode ser realizada com a régua milimétrica, compasso de Willis, paquímetro (AL-ANI e GRAY 2004), ou com os próprios dedos do paciente (ZAWAWI et al. 2003).

Na literatura, a incidência média do trismo radioinduzido em pacientes com CCP costuma oscilar em torno de 55% (GOLDSTEIN et al. 1999; KENT et al. 2008; BENSADOUN et al. 2010; JOHNSON et al. 2010; WEBER et al. 2010). Alguns estudos indicam uma redução da incidência do trismo com a IMRT (TEGUH et al., 2008; HSIUNG et al 2008; CHEN et al 2011), pois esta técnica permite a administração de doses mais baixas de radiação para o tecido normal em comparação com a RT2D e a RT3D (TRIBIUS e BERGELT, 2011). Muitos são os estudos que relatam menor incidência de xerostomia e hipossialia em pacientes tratados com a IMRT devido à redução de dose de irradiação sobre as glândulas parótidas (BRAAKSMA et al., 2003; KAM et al., 2003; LEE et al., 2007, VERGEER et al., 2009), porém quanto à incidência de trismo radioinduzido em pacientes com CCP a literatura científica encontrada é contraditória (TEGUH et al., 2008; KENT et al., 2008, ZHANG et al 2009; CHEN et al. 2011).

Mesmo sob baixas doses de irradiação o trismo pode ocorrer durante o tratamento radioterápico (GOLDSTEIN et al. 1999; BRAGANTE et al. 2012) principalmente se a funcionalidade do paciente estiver reduzida (JOHNSON et al. 2010; BRAGANTE et al. 2012) e os campos irradiados incluírem a boca e/ou orofaringe (GOLDSTEIN et al. 1999; WEBER et al. 2010). Porém, sua incidência aumenta proporcionalmente ao aumento da dosagem de irradiação (RIDDER 1993; TEGUH et al. 2008) e após o término do tratamento (ICHIMURA e TANAKA 1993; SALAZAR et al. 2008).

Os estudos realizados com protocolos de preservação de órgãos vêm mostrando taxas de sobrevida semelhantes ao tratamento cirúrgico convencional (CINTRA et al. 2005; LAZARUS 2006; TEGUH et al 2008), entretanto, esta preservação da anatomia não garante manutenção adequada da função (CINTRA et al. 2005). BHRANY et al. (2007, p.1955) afirmam que “os médicos que cuidam desses pacientes (CCP) devem contemplar o início precoce, se não profilático, de fisioterapia nos doentes com maior risco para o desenvolvimento de trismo (....)”.

Questão importante levantada por LERA et al. (2011) é que pacientes oncológicos submetidos a freqüentes procedimentos apresentam altos níveis de estresse, portanto, intervenção fisioterápica, durante o período de irradiação, somente deve ser realizada se comprovadamente efetiva na prevenção do trismo, evitando assim tornar-se mais um fator

desencadeante de estresse nesses pacientes. Assim sendo, é prudente identificar os fatores de risco para trismo (SANTOS et al. 2010) para que somente pacientes potenciais realizem intervenções preventivas diárias com fisioterapeutas, enquanto os de menor risco apenas recebam orientações de exercícios domiciliares.

Todos os profissionais envolvidos no cuidado e tratamento dos pacientes com CCP, como médicos, enfermeiros, técnicos de enfermagem, fonoaudiólogos e dentistas, deveriam estar capacitados, portanto, no aconselhamento informal dos pacientes irradiados para instituição de medidas preventivas e reconhecimento de pacientes potenciais ao desenvolvimento de trismo radioinduzido para encaminhá-los ao fisioterapeuta, tornando possível intervenções imediatas que repercutirão na QV desses pacientes.

1.3.2 Tratamento do trismo radioinduzido

Como já relatado, diversos são os profissionais da saúde envolvidos no cuidado do paciente com CCP, dessa forma, várias modalidades de tratamento para o trismo radioinduzido têm sido indicadas por diferentes especialidades de profissionais.

De acordo com as duas revisões sistemáticas existentes na literatura sobre o assunto (DIJKSTRA et al. 2004; BENSADOUN et al. 2010), os efeitos das intervenções terapêuticas no trismo radioinduzido são mal investigados. Alguns recursos, como a oxigenioterapia hiperbárica e o uso de pentoxifilina via oral, demonstraram nenhuma e apenas uma modesta eficácia, respectivamente (KING et al. 1989; CHUA et al. 2001). Um relatório sobre a eficácia da toxina botulínica injetada nos masseteres de pacientes com dor e trismo induzidos por radiação não demonstrou melhora significativa no trismo, mas demonstrou uma redução significativa da dor local (HARTL et al. 2008). Por outro lado a coronoidectomia demonstrou eficácia significativa em um estudo não controlado em pacientes com CCP com trismo refratário a fisioterapia, embora essa seja uma técnica invasiva, trazendo riscos cirúrgicos elevados em pacientes irradiados (BHRANY et al. 2007).

1.3.3 Fisioterapia no trismo radioinduzido

A fisioterapia é considerada a base do tratamento e prevenção do trismo radioinduzido, apresentando baixo risco, porém sua efetividade não foi ainda devidamente estabelecida na literatura (STUBBLEFIELD et al. 2010).

O tratamento com a fisioterapia no trismo radioinduzido inclui técnicas de massoterapia, alongamentos passivos e ativos e o uso de dispositivos terapêuticos com o objetivo de liberar aderências restaurando os movimentos mandibulares através de um aumento da amplitude de movimento (ADM) da ATM (SCHULTZ e SOUZA 2000). As técnicas fisioterapêuticas relatadas na literatura para tratamento do trismo não relacionado à oncologia de cabeça e pescoço incluem movimentos ativos, alongamentos passivos, técnica de contração-relaxamento, distração temporomandibular, massagem intra e extra-oral, eletroterapia e termoterapia (DHANRAJANI e JONAIDEL 2002; BIASOTTO-GONZALEZ 2005; DIJKSTRA et al. 2007). No entanto, alguns desses recursos não são aplicáveis na população oncológica por fatores peculiares à doença. O calor superficial e a eletroterapia, por exemplo, utilizados para analgesia entre outras finalidades, tornam-se recursos contra-indicados em tecidos com sensibilidade e suplemento sanguíneo inadequados, tais como os irradiados, pois podem gerar isquemia e necrose (BARRET et al. 1988).

De acordo com RIDDER (1993), o enfoque da fisioterapia no paciente irradiado com CCP deve ser em prevenir ou restaurar contraturas musculares, recuperar a mobilidade e a coordenação muscular, restabelecer a ADM da mandíbula, do pescoço e da cintura escapular e incentivar a cooperação do paciente junto ao tratamento com os diversos profissionais que o acompanham. Conforme o mesmo autor, o objetivo da fisioterapia, no paciente com trismo, é restaurar a funcionalidade e lhe proporcionar a melhor QV possível. Segundo DIJKSTRA et al. (2007) os exercícios que são freqüentemente propostos para prevenir ou tratar o trismo radioinduzido incluem uma gama de exercícios ativos aliados a variados outros passivos e, geralmente, algumas ferramentas são utilizadas como incentivo para o cumprimento do exercício ou para aumentar a eficácia terapêutica.

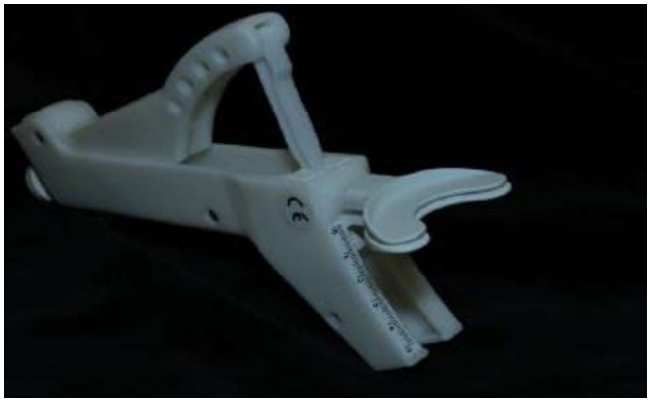
Exercício ativo ocorre quando o movimento é impulsionado pela musculatura ao redor da articulação. Já o exercício passivo ocorre quando uma força externa é aplicada causando movimento da articulação na ausência de atividade muscular (BENSADOUN et al. 2010). Os exercícios ativos citados na literatura para tratamento do trismo incluem abrir e fechar a boca, mover a mandíbula para direita e para esquerda e mover a mandíbula para frente e para trás, com freqüências ao dia, número de repetições e tempo de sustentação do exercício variados (RIDDER 1993; WHYTMYER et al. 1997; DHANRAJANI e JONAIDEL 2002; BENSADOUN et al. 2010).

O exercício passivo para alongamento da musculatura mastigatória pode ser realizado pelo fisioterapeuta, que, com luvas, após o paciente abrir a boca, posiciona o polegar nos incisivos centrais superiores, cruzando o indicador em direção aos incisivos centrais inferiores

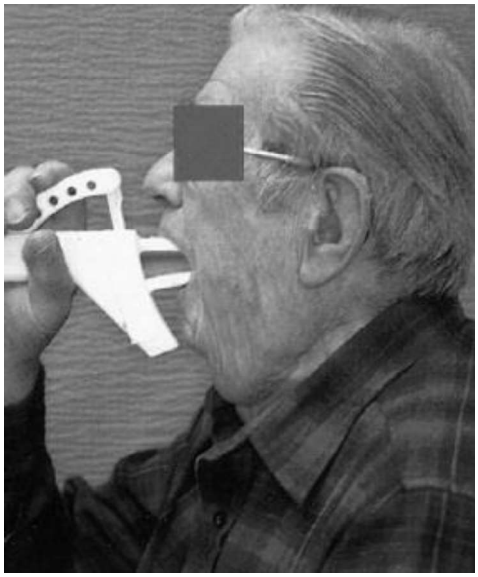
do paciente, o que permitirá a alavanca necessária para forçar a AB (RIDDER 1993). Tal manobra também pode ser realizada pelo próprio paciente (WHYTMYER et al. 1997) ou através de dispositivos que permitem o alongamento passivo (BENSADOUN et al. 2010).

As ferramentas terapêuticas mais citadas na literatura para aumentar a eficácia da fisioterapia no ganho de ADM mandibular do paciente serão descritas a seguir:

- Therabite (Figuras 1 e 2): é um dispositivo de plástico que é colocado na boca e atua com a aplicação de força manual através de alavancas de plástico. A força de abertura é proporcional ao quão rígidas às alavancas do dispositivo são apertadas. A força é normalmente feita próxima à tolerância máxima do paciente e mantida por sete segundos, sete vezes em sete repetições por dia (STUBBLEFIELD et al. 2010).



Fonte: STUBBLEFIELD et al. (2010)
Figura 1 – Therabite



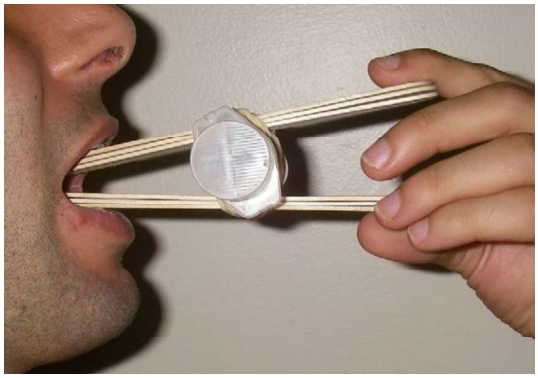
Fonte: COHEN et al. (2005)
Figura 2 – Foto ilustrativa do uso do Therabite

➢ Abaixadores de língua (Figura 3): as espátulas de madeira são empilhadas entre os dentes do paciente, abaixadores adicionais são então introduzidos para o meio da pilha forçando a ADM mandibular (BUCHBINDER et al. 1993).

Fonte: STUBBLEFIELD et al. (2010)
Figura 3 – Abaixadores de língua

➢ "Pat-Bite" (Figura 4 e 5): consiste em 3 abaixadores de língua presos abaixo de uma seringa de 25 ml por uma borracha elástica cruzada a 3 abaixadores de língua sobre a seringa. Com uma extremidade das espátulas na boca o paciente pressiona a outra extremidade que atua como uma alavanca para ajudar na abertura bucal (MEHANNA 2010).

Fonte: MEHANNA (2010)
Figura 4 – "Pat-Bite"



Fonte: MEHANNA (2010)
Figura 5 – Foto ilustrativa do uso do "Pat-Bite"

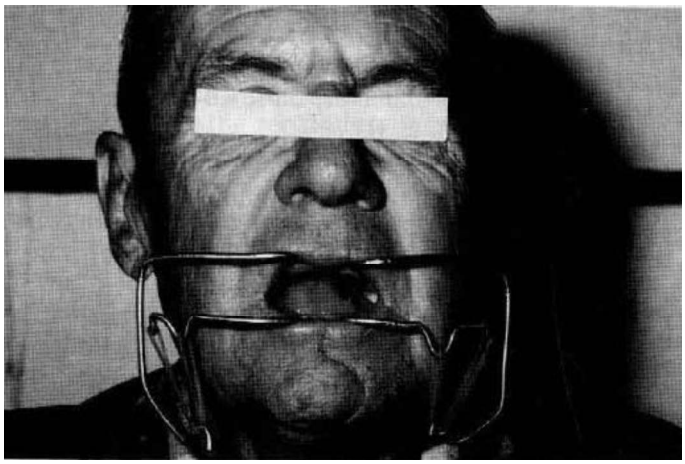
➢ Dynasplint Trismus System – DTS (Figuras 6 e 7): dispositivo de mobilização dinâmica da mandíbula comercialmente disponível, porém com as bandejas bucais personalizadas para o paciente possibilitando mãos livres. Possui um sistema de tensão reprodutível, calibrado e modificável conforme a necessidade do paciente, produzindo um alongamento de baixo torque com o objetivo de atingir a duração de 90 minutos ao dia (SHULMAN et al. 2009).

Fonte: SHULMAN et al. (2009)
Figura 6 – *Dynasplint Trismus System*

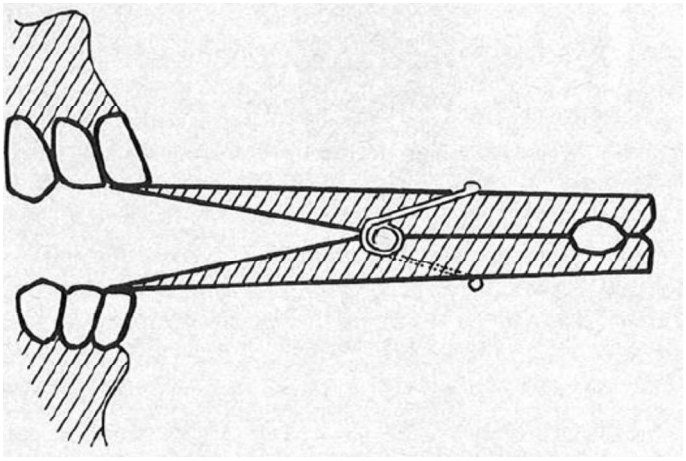
Fonte: DYNASPLINT SYSTEMS 2011
Figura 7- Foto ilustrativa do uso do *Dynasplint Trismus System*

Outras ferramentas terapêuticas como a goma de mascar (SANTOS 2003; GRANDI et al. 2007) e o cone de borracha (Figura 8) também atuam em adjuvância com a fisioterapia convencional para tratamento do trismo radioinduzido. Diversos abridores dinâmicos de mordida são descridos e defendidos através de relatos de caso na literatura, muitos desses dispositivos são complexos, demorados e caros para construir (LUND e COHEN 1993), outros apesar da simplicidade são volumosos e trazem preocupação ao paciente quanto a sua aparência (Figura 9), há também os dispositivos improvisados como os prendedores de roupa (Figura 10) e os incomuns como a "gravata com peso" (Figura 11).

Fonte: STUBBLEFIELD et al. (2010)
Figura 8 - Cone de borracha



Fonte: BRUNELLO e MANDIKOS (1995)
Figura 9 – Modelo de abridor dinâmico da mandíbula



Fonte: WERNER (1974)
Figura 10 – Utilização do prendedor de roupa para aumento da abertura bucal

Fonte: ABDEL-GALIL et al. (2007)
Figura 11 - Foto com a utilização da “gravata com peso”

Todos os dispositivos acima descritos mostraram-se beneficiar o aumento da AB em estudos e séries de casos (WERNER 1974; LUND e COHEN 1993; BRUNELLO e MANDIKOS 1995; ABDEL-GALIL et al. 2007; DIJKSTRA et al. 2007; LO et al. 2008; SHULMAN et al. 2009; MEHANNA 2010). Apesar do uso generalizado desses dispositivos, a literatura é limitada sobre a fisioterapia no tratamento do trismo radioinduzido (DIJKSTRA et al. 2004; BENSADOUN et al. 2010) e a maioria dos procedimentos preventivos descritos é baseada na experiência clínica, uma vez que existe um número restrito de ensaios clínicos relatados na literatura, e os que existem apresentam resultados contraditórios (GRANDI et al. 2007; CARNABY-MANN et al. 2012 LOORENTS et al. 2014).

O estudo de GRANDI et al. (2007) teve como objetivo prevenir o trismo radioinduzido através de dois regimes terapêuticos diferentes. Cinqüenta e quatro pacientes do Sistema Único de Saúde do Serviço de Radioterapia do Hospital Santa Rita do Complexo Hospitalar Santa Casa de Misericórdia de Porto Alegre, foram distribuídos em 3 grupos: Grupo controle - não realizou exercícios; Grupo 1 - realizou o protocolo de BUCHBINDER et al. (1993) que consistia em seis vezes ao dia realizar 10 repetições de exercícios de abrir e fechar a boca, lateralização direita e esquerda e protusão mandibular; Grupo 2 - realizou o protocolo de SANTOS (2003) que consistia em três vezes ao dia realizar 5 repetições de exercícios de abrir e fechar a boca, lateralização direita e esquerda, protusão mandibular e após mascar dois *Tridents* por 15 min. Os exercícios foram realizados diariamente em domícilio, sem supervisão, durante o tratamento com a terapia de irradiação. RT2D foi empregada em todos os pacientes. Como resultado, a AB mostrou uma tendência de redução em todos os grupos, mas sem significância estatística. Não houve diferença estatisticamente significativa na medida da AB entre os grupos, mas houve uma tendência do grupo 2 ter melhores resultados. Não foi possível concluir que os exercícios de fisioterapia são eficazes para prevenir o trismo.

O estudo de CARNABY-MANN et al. (2012) teve como objetivo principal à profilaxia da função da deglutição analisando a AB como desfecho secundário. Cinqüenta e oito pacientes foram divididos em três grupos: Grupo exercício com therabite, que fez referência ao estudo de BUCHBINDER et al. (1993) onde os alongamentos eram realizados em 5 séries de 30s com o Therabite 6x/dia, Grupo cuidados habituais que recebeu as orientações de rotina da instituição e Grupo terapia placebo para a deglutição. O grupo Therabite mostrou um declínio significativamente menor na AB em relação aos outros dois grupos.

No estudo de LOORENTS et al. (2014) sessenta e seis pacientes consecutivos de duas clínicas de radioterapia da Suécia foram randomizados em dois grupos para possível prevenção do trismo radioinduzido: exercícios com Therabite, que consistiam em realizar cinco vezes ao dia, cinco séries, sustentando 15 segundos o alongamento, ou grupo controle. Aos pacientes do grupo controle que reduzissem a AB mais de 15% da medida do baseline era oferecido trocar para o grupo treinamento. Os pacientes do grupo controle realizaram exercícios por conta própria que não foram padronizados ou relatados no estudo. A técnica radioterápica utilizada foi RT3D e IMRT. A medida de AB foi verificada semanalmente durante o curso da RT. Não foram incluídos no estudo dados sobre mucosite e tipo de

alimentação. Como resultado, os pacientes do grupo controle tiveram aumento médio de 1,7% na AB.

O tempo de alongamento de somente 15 segundos, no estudo de LOORENTS et al. (2014), pode justificar esse melhor resultado no grupo controle, pois esta curta duração de tempo na ADM mandibular máxima resulta em espasmo dos músculos da mastigação (SHULMAN et al. 2009). Haja vista que no estudo de CARNABY-MANN et al. (2012) o grupo que manteve o tempo de alongamento com o uso do *Therabite* em 30 segundos, apresentou uma medida de AB significativamente maior do que os outros grupos. Tal fato pode ser explicado fisiologicamente segundo KISNER e COLBY (2005, p.149):

> "Quando um músculo é alongado muito rapidamente, as fibras aferentes primárias estimulam os motonêuronios alfa da medula espinhal e facilitam a contração das fibras extrafusais, aumentando a tensão no músculo. (....). Se uma força de alongamento lenta é aplicada ao músculo, os órgãos tendinosos de Golgi (OTGs) disparam e inibem a tensão no músculo, permitindo que o componente elástico paralelo (o sarcômero) do músculo permaneça relaxado e se alongue."

Apesar das extensas pesquisas, há ainda discordância quanto ao tempo em que um único ciclo de alongamento deve ser mantido ou quanto ao número de ciclos de alongamento que devem ser aplicados para obter os ganhos mais efetivos e duradouros na ADM (KISNER e COLBY 2005). Parece não haver benefício adicional em manter cada ciclo de alongamento além de 60 segundos (BANDY e IRION 1994).

2 JUSTIFICATIVA

O avanço tecnológico nos tratamentos radioterápicos tem aumentado a sobrevida dos pacientes portadores de CCP, embora ainda sob efeitos colaterais indesejados, demonstrando a importância de levar-se em consideração o impacto da RT sobre aspectos funcionais e estéticos. A apropriada prevenção e o tratamento das complicações da RT são necessários, reduzindo assim comorbidades nesses pacientes com maiores expectativas de vida.

Devido a dados contraditórios e a falta de evidência na literatura científica quanto à efetividade das técnicas fisioterapêuticas na prevenção do trismo radioinduzido, verifica-se a necessidade de melhor investigar a eficácia e o impacto na QV de diferentes técnicas fisioterapêuticas profiláticas para o trismo radioinduzido em pacientes com CCP.

3 OBJETIVOS

3.1 OBJETIVO GERAL

Verificar o efeito de dois protocolos de exercícios fisioterapêuticos na manutenção da amplitude de movimento mandibular em pacientes com CCP em tratamento radioterápico.

3.2 OBJETIVOS ESPECÍFICOS

- Comparar os valores de abertura, protusão e excursões laterais da mandíbula, obtidos no período pré e pós-RT, entre os grupos intervenção;
- Comparar os valores de abertura, protusão e excursões laterais da mandíbula, obtidos no período pré e pós-RT, entre os grupos intervenção e o grupo controle;
- Comparar os valores de abertura, protusão e excursões laterais da mandíbula, obtidos no período pré e pós-RT, em cada grupo;
- Comparar os valores da *Karnofsky Performance Status* (KPS) obtidos no período pré e pós-RT entre os três grupos;
- Comparar o escore total do questionário de QV no período pré e pós-RT entre os três grupos;
- Verificar quais variáveis demográficas e clínicas associam-se com a manutenção, redução ou aumento da medida AB;
- Analisar a adesão dos pacientes aos protocolos de exercícios.

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5 DESENVOLVIMENTO

A seção de desenvolvimento será apresentada a seguir na forma de manuscrito, que será submetido à publicação no periódico *"Head & Neck"* e é intitulado: **Exercise therapy to prevent mandibular hipomobility in irradiated patientes with head and neck cancer.**

5.1 MANUSCRITO

Exercise therapy to prevent trismus in irradiated patients with head and neck cancer: a randomized clinical trial

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ABSTRACT

Background: Patients undergoing radiation therapy for head and neck cancer may develop mandibular hypomobility. **Methods**: Ninety patients were randomized into three groups: TheraBite-Hiperboloide exercise group (THEG), Hiperboloide exercise group (HEG), or control (CG). Mandibular mobility was measured before and after radiation therapy. **Results**: In the THEG group, treatment-adherent patients exhibited a mean increase of 2.3 (± 3.9) mm in mouth opening (MO), whereas non-adherent patients experienced a mean MO reduction of 3.9 (± 7.6) mm. This difference was considered significant (p=0.007). In the HEG, although adherent patients experienced less reduction in MO than nonadherent patients, the difference was not significant (p=0.295). After covariance analysis, the variables group allocation (p=0.022) and degree of mucositis (p=0.027) remained associated with change in MO. **Conclusion**: A rehabilitation protocol combining the TheraBite system and chewing exercises with the Hiperboloide device is the most appropriate option for preservation of MO during radiation therapy.

INTRODUCTION

Trismus, or mandibular hypomobility,[1] develops in 38–50% of patients undergoing radiation therapy for head and neck cancer (HNC).[2-5] Trismus may occur during the irradiation period particularly in patients with reduced performance status,[5, 6] when the fields of radiation involve the mouth and/or oropharynx,[2, 6, 7] when radiation is administered postoperatively[4, 8] or in case of reduced masticatory muscle function due to exclusive enteral tube feeding.[6, 9] However, the occurrence of trismus increases proportionally with increasing radiation doses[10] and after completion of radiation therapy, reaching peak incidence at 6 and 9 months,[3, 11] if radiation-induced fibrosis is developing in the masticatory muscles or in the temporomandibular joint (TMJ) region.[12]

The development of trismus has a negative impact on patient quality of life (QoL),[2, 3, 12] as it causes changes in facial appearance, difficulty speaking, problems with denture use and oral hygiene, and difficulty feeding, potentially leading to malnutrition. Nevertheless, there is a dearth of research on the prevention of radiation-induced trismus, and the few studies that have been performed[13-17] did not report satisfactory findings for prophylaxis of this complication. The current evidence suggests that radiation-induced trismus is difficult to treat, and, therefore, efforts should focus on its prevention rather than its management.[18-22]

Some of the therapeutic options for trismus prevention cited in the literature include active jaw exercises,[13, 16] mouth openers[14-17] – particularly the TheraBite® Jaw Motion Rehabilitation System™ (TheraBite)[14, 16, 17] – and chewing gum.[13] However, edentulous patients do not benefit fully from therapeutic use of chewing gum. In Brazil, 20% of the population is completely edentulous,[23] and HNC patients expected to undergo radiation therapy often have several teeth extracted to remove foci of oral infection that might predispose them to complications.[24] Within this context, the Hiperboloide device, a low-cost chew tool used as an adjunct in the treatment of TMJ dysfunction,[25] has the potential for

therapeutic use in patients with HNC. The Hiperboloide device acts on two factors involved in trismus: immobility (as the patient is required to activate stomatognathic system components to chew the device) and muscle performance (by resisting masticatory forces and thus strength-training the muscles of mastication), we hypothesized that its use during radiation therapy (RT) might prevent or minimize the development of mandibular hypomobility, and sought to compare the results of its use with and without TheraBite, in view of the high cost of the latter device.

The primary objective of this study was to assess whether a preventive intervention consisting of therapeutic exercise preserves mandibular range of motion during RT or at least minimizes restriction of range of motion, maintaining a range of mouth opening (MO) close to pretreatment levels, and whether a difference in mandibular mobility exists between patients who exercise with and without the aid of the TheraBite device. The secondary objective was to ascertain whether associations exist between MO outcomes and demographic parameters, clinical variables, and adherence to the study interventions.

MATERIALS AND METHODS

This randomized, parallel-group, controlled clinical trial was registered in ClinicalTrials.gov under accession number NCT02094690.

Study setting and participants

This trial was carried out at the Department of Radiation Oncology of a university hospital in the city of Porto Alegre, Brazil. Between 1 May 2013 and 31 May 2014, we screened all consecutive patients with HNC (neoplasms of the oral cavity, oropharynx, hypopharynx, nasopharynx, larynx, salivary glands, nasal fossa, and paranasal sinuses) undergoing RT who met the following eligibility criteria: either sex; age > 18 years; formal

histopathological diagnosis of HNC; undergoing RT alone or as adjunct to surgery and/or chemotherapy; and who had one or more muscles or mastication or the TMJ involved in the radiation field.

The criteria for exclusion were: motor sequelae affecting the upper extremities, face or neck region, whether secondary to stroke, facial palsy, trigeminal neuralgia, trauma and/or surgery that precluded completion of the exercise protocols; cognitive impairments (proven and noted in the medical record), such as Alzheimer's disease, senile dementia, and/or Wernicke-Korsakoff syndrome, which could impair understanding of the exercise protocols; history of prior RT to the head and neck region; history of surgical interventions involving resection of the mandible or of any of the muscles of mastication; current physical therapy or speech pathology interventions for trismus; initial MO range < 10 mm; Karnofsky Performance Status (KPS)[26] < 60%; and refusal to take part in the study.

Sample size calculation

The sample size was calculated in PEPI (*Programs for Epidemiologists*) 4.0 software, and was based on the studies of Tang et al.[20] and Buchbinder et al.[18] For a significance level of 5%, statistical power of 90%, and between-group effect size of one standard deviation for the primary outcome, the minimum sample size was calculated as 23 patients per group, for a total of 69 patients. To enable multivariate analysis and account for potential attrition, we increased the sample by 30% for a total of 90 patients.

Randomization

Patients were randomly allocated the three study groups, at a ratio of 1:1:1, by random number generation with the RANDOM subroutine of the PEPI software suite. The confidentiality of allocation was ensured by using sealed, numbered, opaque brown paper

envelopes. These enveloped were stored and handled only by a nurse otherwise uninvolved in the study, who was contacted by telephone, at the start of the intervention, by the physical therapist (PT) responsible for patient training.

Blinding

The PT responsible for outcome examination, the radiation oncologists and technologists, and the statistician were all blinded to patient allocation. Only the training PT and each patient were aware of allocation.

Data collection

Patients eligible for inclusion were identified, prior to the start of their radiation therapy regimens, during the weekly multidisciplinary team meetings of the Department of Radiation Oncology. On the day of radiation simulation, patients were informed of the study and invited to participate. After each patient agreed to take part and provided written informed consent, data collection was begun.

A history and physical examination (H&P) was obtained from each patient, individually. H&P was always performed by the same examiner – a trained PT with ample experience in the study protocols – and sought to collect data on the following variables:

Demographic: age, sex, skin color, educational attainment, smoking, drinking, and type of diet (classified as normal/solid, semisolid, liquid, or enteric/gastrostomy tube).[27]

Clinical: tumor site, histological type, concomitant chemotherapy, surgery, tumor stage (according to the Union for International Cancer Control [UICC] TNM classification of malignant tumors),[28] modality and dose of radiation therapy. These data were extracted from patient records.

Physical examination was performed at two time points: before the start of RT (T0) and immediately after the last RT session (T1), and sought to assess the following outcomes: mandibular mobility, oral mucositis, functional capacity, and pain. Weekly reassessments were performed by the training PT throughout the course of RT.

Mandibular mobility was assessed by the parameters maximum mouth opening (MMO), right lateral excursion (RLE), left lateral excursion (LLE), and mandibular protrusion (PR). These parameters were measured using Digimess 100.179N digital calipers (resolution 0.01 mm/.0005", with a certificate of calibration provided by the manufacturer), following the instructions and specifications for clinical examination defined by the Research Diagnostic Criteria for Temporomandibular Disorders (RDC-TMD).[29] The adaptations proposed by Goldstein et al.[7] and Dijkstra et al.[30] for assessment of completely and partially edentulous patients were adopted, namely: in patients with an edentulous mandible and no dentures, the distance between the incisal edge of the verticalmost maxillary central incisor and the opposing (i.e., corresponding mandibular) alveolar ridge was measured; in patients with an edentulous maxilla and no dentures, the distance between the incisal edge of the verticalmost mandibular central incisor and the opposing alveolar ridge was measured; in fully edentulous patients, MO was measured from the mandibular alveolar ridge to the maxillary alveolar ridge along the midline corresponding to the nasopalatine foramen. The condition of the teeth was noted to enable correction in the event of changes.

Oral mucositis was graded in accordance with the World Health Organization (WHO) Oral Toxicity Scale.[31] Functional capacity was measured by the KPS.[26] Pain was assessed using a visual analog scale.[32]

After H&P, patients completed the University of Washington Quality of Life (UW-QOL) Questionnaire, version 4, which is validated for the Brazilian population.[33] Due to the low educational attainment of the Brazilian population, as reported in previous studies,[34] the

examiner read the questionnaire aloud to all patients, without providing any assistance for completion.

Exercise protocols

After assessment, each patient – always chaperoned by a family member – was given a booklet containing written and illustrated instructions on the physical therapy protocol to be followed, as well as verbal guidance provided by the training PT.

As noted above, patients were allocated randomly across three groups: TheraBite-Hiperboloide exercise group (THEG), Hiperboloide exercise group (HEG), and control group (CG). The protocols used in each group were as follows:

THEG: a) warm-up (exercises to enhance joint lubrication): 10x mouth opening and closing, 10x RLE, 10x LLE, 10x PR; b) stretching: 6 sets of holding the TheraBite device at MMO for 30 seconds; c) strength training: 5 minutes of alternating bilateral chewing with a size XS Hiperboloide device. Halfway along the course of RT, the size of the device was increased to S. A new Hiperboloide device was provided each week during the patient's training visit.

HEG: Same warmup and strength training protocol as in THEG, but without the TheraBite stretching step.

CG: Not exposed to either of the tested intervention protocols. However, just as patients in THEG and HEG, controls received pre-RT guidance from the nursing team, which consisted of: avoiding exposure of the irradiated area to sunlight, not shaving with a razor over the irradiated area, cleansing the irradiated area with neutral soap alone, drinking 2 L water daily, and daily mouth rinses and compresses with chamomile (*Matricaria chamomilla*) tea in an attempt to prevent mucositis and dermatitis respectively. Controls did not receive any specific guidance on trismus prevention.

Patients in the exercise groups were instructed to start the exercise protocols one day before the start of RT and continue until the end of RT, performing the protocol exercises four times a day (after breakfast, lunch, dinner, and at bedtime, to prevent missed exercises). Throughout the course of RT, patients performed one supervised exercise session per week, under the guidance of the training PT. Controls also met with the PT for assessment of potential adverse reactions to therapy.

The TheraBite (Figure 1a) is a portable, single-patient use plastic device equipped with mouthpieces that are placed between the maxilla and mandible. The mouthpiece forces the mouth open proportionally to the strength with which the user squeezes the lever of the device. Depending on the condition of the patient's teeth, different bite pads (regular bite pad, edentulous bite pad, or both) are used. These foam pads were fitted to the TheraBite by the training PT, taking into account the patient's dentition.

The Hiperboloide (Figure 1b) is a peri-myofunctional exercise device consisting of a non-toxic, odorless, and tasteless Silastic hyperboloid, which comes in five different sizes. To ensure the safety of therapy with this device, a length of dental floss was threaded through the body of the device so that patients could hold it securely during chewing exercises, as recommended by the manufacturer.

Protocol adherence

To assess protocol adherence, at T0, each patient was given a training log on which to record his or her exercise progress. These logs were designed for easy completion, so enable their use by patients with low educational attainment, and covered the whole duration of the RT course.

Adherence was classified as high (patients who completed their protocol exercises at least twice daily), moderate (patients who completed their protocol exercises up to twice daily

and missed their exercises no more than 1 day per week), low (patients who missed their exercises no more than 2 days per week), or absent (patients who missed or skipped their exercises on 3 or more days per week).

Oncologic treatment

All patients underwent external photon beam radiotherapy, at a dose of 2 Gy per fraction per day, 5 days a week, over a 5- to 7-week course of therapy, for a final dose ranging from 50 to 70 Gy. Overall, 61 patients (68.5%) received concomitant chemotherapy (50 mg cisplatin once weekly), and one (1.1%) received targeted therapy (cetuximab) in addition to chemotherapy. Treatment regimens were individualized according to tumor site, size, and stage.

The present study was conducted in accordance with the ethical standards of the Declaration of Helsinki and with Brazilian National Health Council Resolution 466/12, and was approved by the Research Ethics Committee of Irmandade Santa Casa de Misericórdia de Porto Alegre with judgment number 259.691.

Statistical analysis

Quantitative variables were expressed as means and standard deviations or as medians and interquartile ranges, depending on the normality of distribution. Categorical variables were expressed as absolute and relative frequencies. The Shapiro–Wilk test was used to assess the distribution of variables.

All randomized patients were included in the intent-to-treat analysis. One-way analysis of variance (ANOVA) with Tukey's post-hoc test was used to compare means across groups. In case of asymmetric distribution, the Kruskal–Wallis test and Mann–Whitney *U*

were used instead. Student's *t*-test for paired samples was used to compare pre- and post-RT parameters.

Pearson's chi-square test with adjusted residuals was used to compare proportions across the study groups. Pearson's linear (r) or Spearman's (r_s) correlation coefficients were used as appropriate, depending on data distribution, to test for associations between quantitative variables.

Analysis of covariance (ANCOVA) with Bonferroni adjustment was used to control for potential confounders. Variables with $p<0.20$ on bivariate analysis were included in ANCOVA.

The significance level was set at 5% ($p<0.05$), and all analyses were carried out in SPSS 21.0.

RESULTS

During the study period, 133 patients with HNC were treated at our Department of Radiation Oncology. Of these, 43 were ultimately excluded, as shown in the CONSORT[35] flow diagram (Figure 2).

All three study groups were homogeneous in terms of demographic and clinical variables at baseline (Table 1 and Table 2 respectively).

Regarding jaw mobility, KPS, mucositis, and pain (Table 3), there was a trend toward reduction of MO in all groups. The least amount of reduction was observed in THEG, although the difference did not reach statistical significance. On within-group analysis, the reduction in MO from baseline was statistically significant in the control group ($p=0.015$). A significant reduction in KPS from baseline was observed in all groups ($p<0.005$), with no within-group significance. Mucositis increased significantly in all groups ($p<0.02$); in THEG,

this increase was significantly greater than in CG. Pain increased significantly in THEG (p<0.001) and HEG (p=0.020), but there was no significant difference among the three groups.

Composite UW-QOL scores declined significantly from baseline in all groups (p<0.02), but again there was no significant difference among the three groups (p=0.067). Variation in composite UW-QOL score was significantly associated with reduction in KPS across all three groups, as shown in Figure 3.

Patients who underwent surgery experienced a greater reduction in MO over the course of RT than patients who did not undergo surgical intervention (-3.2 ± 6.9 vs. -0.4 ± 5.9; p=0.043).

Comparison of the largest patient subgroups by tumor site showed that patients with oral and oropharyngeal cancer experienced greater reductions in MO (-2.68 ± 6.63) than patients with laryngeal and hypopharyngeal cancers (0.20 ± 5.31) (p=0.045).

There was no significant difference in the change in MO between patients who continued to consume alcohol or smoke and those who quit these habits (p=0.732), and no difference between patients who received concomitant chemotherapy and those who did not (p=0.150).

Tumor stage (p=0.310) and modality of RT (p=0.427) – i.e., intensity-modulated RT (IMRT) and three-dimensional conformed RT (3D-RT) vs. conventional two-dimensional RT (2D-RT) – were not associated with change in MO.

Analysis of treatment adherence showed no significant differences between THEG and HEG patients (p=0.371). Among THEG and HEG patients, adhesion was high in 9 (30%) and 15 (50%) respectively, moderate in 8 (26.7%) and 6 (20%) respectively, low in 5 (16.7%) and 2 (6.7%) respectively, and absent in 8 (26.7%) and 7 (23.3%) respectively. Analysis of change in MO as a function of treatment adherence (Figure 4) showed that THEG patients who were treatment-adherent experienced a mean increase in MO of 2.3 ± 3.9 mm, whereas those who

were not treatment-adherent experienced a mean reduction in MO of 3.9 ± 7.6 mm (p=0.007). Among HEG patients, those who were treatment-adherent experienced less of a reduction in MO (-0.91 ± 6.40) than nonadherent ones (-3.5 ± 5.6), but the difference was not significant (p=0.295).

Multivariate ANCOVA was used to control for confounders. On multivariate analysis, only the following variables remained associated with change in MO: group allocation (p=0.022) and severity of mucositis (p=0.027). THEG patients exhibited less change in MO (0.50 ± 1.28) than controls (-3.78 ± 1.25). HEG patients (-2.10 ± 1.50) did not differ significantly from those in either the THEG or the CG. These differences were adjusted for mucositis, feeding type, group allocation, surgery, and tumor site.

Severity of mucositis was also independently associated with MO. The greater the severity of mucositis, the greater the reduction in MO.

Feeding type was significantly associated with MO (p<0.001). This difference remained significant after adjusting for mucositis and group allocation (p=0.002). Adjusted means are shown in Figure 5.

DISCUSSION

We observed a trend toward reduction of MO in all groups in our sample, as reported in other prospective studies of prevention of mandibular hypomobility during RT.[13, 16, 17] However, unlike Loorents et al.,[14] who observed a significant increase in MO in controls, and Ahlberg et al.,[15] who found an increased risk of MO reduction in their rehabilitation group, we observed significant reductions in MO among patients who did not perform preventive exercises. This corroborates the findings of van der Molen et al.[16] and Carnaby-Mann et al.[17]

This difference between our findings and those of Loorents et al.[14] and Ahlberg et al.[15] may be explained by the trismus prevention protocols used. In the Loorents et al. study,

patients in the TheraBite group performed stretching exercises (five sets of 15 seconds) five times a day and controls performed non-standardized exercises; patients in the control group who experienced a > 15% reduction in MO crossed over to the TheraBite group. In the Ahlberg et al. study, patients in the rehabilitation group performed stretching exercises (MMO for 10 sets of 20 seconds) twice daily with the "Acute Medic Jaw Trainer and Stretcher" device; in some patients, the protocol was changed to a "hold and release" technique. Furthermore, control patients (no exercise) were recruited from a different RT center, which may have introduced a selection bias, as the RT modalities employed were not described. We believe that, in these two studies, controls experienced results superior to those of rehabilitated patients due to insufficient stretching time, which may actually induce spasm of the muscles of mastication. It is widely known that, when a muscle is stretched too quickly, type Ia (primary afferent) fibers stimulate alpha motor neurons in the spinal cord, facilitating contraction of extrafusal fibers and generating increased tension in the muscle.[36]

Studies that employed physiological stretching[16,17] observed better results in rehabilitated patients than in controls. When a muscle is stretched slowly, the Golgi tendon organs (GTOs) fire, inhibiting generation of tension in them muscle and allowing the parallel elastic components of the muscle to remain relaxed and stretch.[36] The matter of slow versus fast stretching is an important issue in protocols for management of trismus, as studies that employed protocols using a 30-second duration of stretching obtained better results[18, 21] than studies employing shorter periods of stretching.[20]

Disagreements remain as to how long each cycle of stretching should be sustained. The literature[37, 38] focuses on the duration of stretching in large muscle groups; further research is required to assess this parameter in the muscles of mastication. As noted above, 30 seconds appears to be the most effective duration of a stretching cycle.[39]

The Grandi et al. study[13] also observed a trend toward reduction in MO, but without significant between-group differences. In this study, patients were allocated across three groups: control (no exercise); Group 1 – free active exercises, which consisted of 10x MO, RLE, LLE, and PR, six times a day; and Group 2, which consisted of 5x MO, RLE, LLE, and PR, followed by chewing two pieces of Trident® gum for 15 minutes.[13] We believe 15 minutes of mastication is an excessively long period and may have had a negative impact on the results of the study. As they often have poor dentition and mucositis, patients with HMC are usually on a soft/semisolid diet or enteral feeding, which suppresses the proprioceptive mechanisms involved in preservation of muscle activity; therefore, their hypoactive muscles of mastication require shorter chewing periods to prevent fatigue.[40] The jaw elevator muscles are generally fatigue-resistant, a property attributed to their rich blood supply and high proportion of type I fibers.[41] However, RT can affect local perfusion, and studies[42, 43] have shown that a progressive reduction in muscle activity, as measured by electromyography, occurs after 3 minutes of continuous mastication; even healthy patients report muscle fatigue with longer periods of chewing. Thus, we advise that the duration of mastication exercises should be observed carefully by the PT, especially in patients on exclusive parenteral or enteral feeding, and should not exceed 5 minutes.

The normal range of jaw mobility is 40–70 mm for MO and 8–12 mm for lateral excursions.[44, 45] However, these ranges may vary according to factors such as gender, age, body weight, height, dentition, and presence of signs and symptoms of TMJ dysfunction.[45] The present study did not establish a cutoff MO value for trismus. We believed comparison of the range of jaw motion at different points in time would provide a more reliable estimate, as this would enable identification of any preexisting restrictions in jaw range of motion (whether inherent to the patient or secondary to tumor or surgery) before the start of RT, thus ensuring that only changes attributable to irradiation would be analyzed.

Several studies that analyzed KPS[3, 5, 6] and QoL[2, 3, 15, 46] in irradiated patients with HNC found reductions in these variables after cancer treatment. Likewise, in our sample, patients in all groups experienced reductions in performance status and QoL score, which suggests that a trismus prophylaxis protocol alone is not enough to maintain these variables at pretreatment levels. We observed a direct association between reduction in performance score and reduction in QoL. Further research should investigate whether early, comprehensive physical rehabilitation can have beneficial effects on the functional capacity and QoL of patients with HNC.

The incidence of mucositis in irradiated patients with HNC is approximately 80%.[47] In our study, the incidence of oral mucositis ranged from 40% to 66.7% across groups, and was significantly higher in THEG patients than in controls. We attribute this difference to chance, but future studies should analyze the impact of the TheraBite device not only on MO, but also on the mucosa. As reduction in MO range was directly associated with increasing severity of mucositis and patients in the THEG still experienced the least reduction in MO, we consider this result to be favorable overall. Pain increased significantly in THEG and HEG, which were also the groups with the highest incidence of mucositis. Exercise may worsen the pain of mucositis due to tissue stretching. In the van der Molen et al. study,[16] male patients in the rehabilitation group also experienced significantly more pain. Further research should investigate whether adequate protocols for prevention and treatment of mucositis minimize exercise-related pain in these patients.

In our sample, patients undergoing surgery, those with oral and oropharyngeal tumors, and those with altered dietary consistency experienced greater reductions in range of MO; this corroborates the findings of several previous studies on risk factors for trismus.[2-4, 6] However, we found no association between continued alcohol intake,[4, 48] concomitant chemotherapy,[22] tumor stage,[2, 5] or RT modality[49] and reduction in MO.

In the present study, THEG patients who adhered to the treatment protocol experienced a significant increase in MO as compared with nonadherent patients. HEG patients who were adherent experienced less of a reduction in MO than nonadherent ones, although the difference was not statistically significant. It is known that adherence to exercise protocols is an extremely important determinant of the success of therapy.[50] We found no differences in adherence between THEG and HEG, and over half of all patients in these two groups recorded high or moderate adherence. Traditionally, rehabilitation is started only when loss of function has already occurred. The fact that prophylactic protocols seek to preserve rather than restore function and that, unlike in treatment protocols, patients do not experience noticeable improvement in MO may be a demotivating factor. Therefore, patient education activities should focus on developing a sense of responsibility for one's own health and imparting awareness of the risks of nonadherence to prevention protocols. Another aspect that should be considered is the importance of achieving optimal results without overburdening patients who are already undergoing strenuous cancer treatment. Therefore, repetition of exercises two to four times daily appears reasonable, as demonstrated by moderate to high adherence in the majority of our patients. This corroborates the findings of van der Molen et al.[16]

After multivariate analysis, the only factors associated with change in MO were group allocation and severity of mucositis. This indicates that THEG patients exhibited the range of MO closest to pretreatment levels and that severity of mucositis independently interferes with MO. Thus, further studies should investigate whether prevention of mucositis has an impact on the range of MO of patients undergoing RT for head and neck neoplasms.

Study limitations

One major limitation of this study was the lack of supervision of home exercises. However, training schedules and a weekly therapy session with the training PT were used to mitigate this limitation. The duration of follow-up was also limited. Long-term studies of the effect of exercise protocols on mandibular hypomobility are needed to investigate the persistence of achieved results and the potential deterioration of improvements over time. Finally, the relatively small number of patients treated with IMRT (n=7) and 3D-RT (n=7) hinders interpretation of the results observed in this subgroup, due to a lack of statistical power.

CONCLUSION

We conclude that a rehabilitation protocol that combines use of the TheraBite device and chewing exercises with the Hiperboloide device is most appropriate for preservation of range of mouth opening during RT, rejecting our hypothesis that chewing exercises with the Hiperboloide device alone would minimize mandibular hypomobility.

All members of the multidisciplinary team should be aware of the potential for increased pain and mucositis and should intervene as early as possible when these events occur. Neither of the prophylaxis protocols tested in this study was able to prevent declines in performance status (KPS) or QoL.

Patients with oral and oropharyngeal tumors, those who underwent surgery, those who developed mucositis, and those who were on liquid diet or enteral feeding experienced the greatest reductions in MO.

Treatment adherence is an essential determinant of the success of trismus prevention protocols in patients undergoing RT for head and neck neoplasms.

Longer follow-up of these patients is necessary to ascertain whether the beneficial effects of exercise protocols on MO persist in the post-radiotherapy period. Studies assessing

whether implementation of mucositis prevention protocols have an impact on MO and cost-benefit analyses of therapy with the TheraBite device are also advised.

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TABLES

Table 1. Sample profile

Variable*	Overall (n=90)	CG (n=30)	THEG (n=30)	HEG (n=30)	*p*
Age (years)	57.3 ± 10.3	58.5 ± 12.5	54.7 ± 9.8	58.7 ± 8.0	0.243†
Sex					0.919‡
Male	76 (84.4)	26 (86.7)	25 (83.3)	25 (83.3)	
Female	14 (15.6)	4 (13.3)	5 (16.7)	5 (16.7)	
Skin color					0.626‡
White	64 (71.1)	22 (73.3)	19 (63.3)	23 (76.7)	
Black	10 (11.1)	4 (13.3)	3 (10.0)	3 (10.0)	
Brown	16 (17.8)	4 (13.3)	8 (26.7)	4 (13.3)	
Educational attainment (years of schooling)	5 (4 – 8)	5 (4 – 8)	5 (4 – 8)	6 (4 – 11)	0.524§
Smokers	78 (86.7)	27 (90.0)	26 (86.7)	25 (83.3)	0.749‡
Duration of smoking (years)	36.9 ± 12.3	38.8 ± 12.2	35.9 ± 10.2	35.7 ± 14.3	0.591†
Pack-years	54.9 ± 36.9	52.3 ± 33.6	57.3 ± 39.9	55.4 ± 38.4	0.889†
Drinkers	59 (65.6)	19 (63.3)	20 (66.7)	20 (66.7)	0.952‡
Duration of alcohol intake (years)	29.8 ± 12.3	30.2 ± 15.7	29.2 ± 8.7	30.1 ± 12.5	0.958†
Continues to smoke	25 (32.1)	5 (18.5)	10 (37.0)	10 (41.7)	0.166‡
Continues to drink	3 (4.4)	1 (4.3)	1 (4.5)	1 (4.3)	0.999‡
Diet at T0					0.494‡
Normal/Solid	55 (61.1)	15 (50.0)	22 (73.3)	18 (60.0)	
Semisolid	20 (22.2)	7 (23.3)	6 (20.0)	7 (23.3)	
Liquid	4 (4.4)	2 (6.7)	1 (3.3)	1 (3.3)	
Enteral	11 (12.2)	6 (20.0)	1 (3.3)	4 (13.3)	

CG, control group; HEG, Hiperboloide exercise group; THEG, TheraBite-Hiperboloide exercise group; *Expressed as mean ± standard deviation, median (interquartile range), or n (%);

† Analysis of variance (ANOVA);

‡ Pearson's chi-square test;

§ Kruskal–Wallis test.

Table 2. Clinical profile of sample

Variable	Overall (n=90)	CG (n=30)	THEG (n=30)	HEG (n=30)	$p^{\ddagger}$
Tumor site					0.652
OC, tongue	8 (8.9)	4 (13.3)	2 (6.7)	2 (6.7)	
OC, floor of mouth	5 (5.6)	2 (6.7)	2 (6.7)	1 (3.3)	
OC, retromolar trigone	3 (3.3)	0 (0.0)	2 (6.7)	1 (3.3)	
Oropharynx, tonsils	8 (8.9)	2 (6.7)	3 (10.0)	3 (10.0)	
Oropharynx, base of tongue	14 (15.6)	4 (13.3)	4 (13.3)	6 (20.0)	
Oropharynx, soft palate	7 (7.8)	2 (6.7)	3 (10.0)	2 (6.7)	
Oropharynx, vallecula	1 (1.1)	0 (0.0)	1 (3.3)	0 (0.0)	
Nasopharynx	4 (4.4)	2 (6.7)	0 (0.0)	2 (6.7)	
Hypopharynx, pyriform sinus	12 (13.3)	2 (6.7)	7 (23.3)	3 (10.0)	
Hypopharynx, pharyngeal wall	2 (2.2)	0 (0.0)	0 (0.0)	2 (6.7)	
Nasal fossa	2 (2.2)	1 (3.3)	1 (3.3)	0 (0.0)	
Paranasal sinuses	1 (1.1)	1 (3.3)	0 (0.0)	0 (0.0)	
Salivary gland, parotid	4 (4.4)	1 (3.3)	1 (3.3)	2 (6.7)	
Salivary gland, submandibular	1 (1.1)	0 (0.0)	0 (0.0)	1 (3.3)	
Larynx, supraglottic	17 (18.9)	9 (30.0)	4 (13.3)	4 (13.3)	
Larynx, glottic	1 (1.1)	0 (0.0)	0 (0.0)	1 (3.3)	
Histological type[†]					0.305
Spindle cell carcinoma	83 (94.3)	29 (96.7)	28 (93.3)	26 (92.9)	
Adenoid cystic carcinoma	2 (2.3)	0 (0.0)	0 (0.0)	2 (7.1)	
Acinic cell carcinoma	2 (2.3)	1 (3.3)	1 (3.3)	0 (0.0)	
Verrucous carcinoma	1 (1.1)	0 (0.0)	1 (3.3)	0 (0.0)	

Variable	Overall (n=90)	CG (n=30)	THEG (n=30)	HEG (n=30)	*p*‡
Chemotherapy	61 (68.5)	18 (60.0)	20 (66.7)	23 (79.3)	0.269
Surgery	43 (47.8)	15 (50.0)	18 (60.0)	10 (33.3)	0.113
Neck dissection	35 (38.9)	14 (46.7)	12 (40.0)	9 (30.0)	0.411
Stage					0.556
I	3 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	
II	9 (10.0)	1 (3.3)	3 (10.0)	5 (16.7)	
III	25 (27.8)	8 (26.7)	11 (36.7)	6 (20.0)	
IVA	53 (58.9)	20 (66.7)	15 (50.0)	18 (60.0)	
RT modality					0.456
IMRT	7 (7.8)	2 (6.7)	1 (3.3)	4 (13.3)	
2D	76 (84.4)	25 (83.3)	28 (93.3)	23 (76.7)	
3D	7 (7.8)	3 (10.0)	1 (3.3)	3 (10.0)	
RT dose	50 (44 – 70)	50 (44 – 62)	60 (44 – 70)	56 (50 – 70)	0.203§

OC, oral cavity; CG, control group; HEG, Hiperboloide exercise group; THEG, TheraBite-Hiperboloide exercise group; IMRT, intensity-modulated radiation therapy; RT, radiation therapy; 3D, three-dimensional conformed radiation therapy; 2D, two-dimensional conventional radiation therapy;

***** Expressed as mean ± standard deviation, median (interquartile range), or n (%);

† Data missing for two patients in the HEG;

‡ Pearson's chi-square test;

§ Kruskal–Wallis test.

Table 3. Comparative analysis of mandibular mobility across groups

Variable	CG (n=30)	THEG (n=30)	HEG (n=30)	*p*
Mouth opening (mm)				
Pre	42.5 ± 10.7*	42.4 ± 12.3	43.3 ± 11.2	0.940§
Post	39.3 ± 10.8	42.0 ± 12.8	41.6 ± 11.7	0.630§
Change (Δ)	-3.2 ± 6.8	-0.4 ± 6.5	-1.7 ± 6.2	0.246§
RLE (mm)				
Pre	5 (0 to 10)	5 (0 to 8.5)	5.5 (0 to 10)	0.538‡
Post	5 (1.5 to 10)	5 (0 to 10)	5 (0 to 10)	0.677‡
Change (Δ)	0.0 (-0.3 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.915‡
LLE (mm)				
Pre	5.5 (0 to 10)	5 (0 to 10)	6 (0 to 10)	0.494‡
Post	6 (1.5 to 10)	5 (0 to 10)	5 (0 to 10)	0.670‡
Change (Δ)	0.0 (-0.3 to 0.0)	0.0 (0.0 to 0.0)	0.0 (-2.0 to 0.0)	0.583‡
PR (mm)				
Pre	3 (0 to 4.3)	2 (0 to 5)	2.5 (0 to 6)	1.000‡
Post	2 (0 to 4)	2 (0 to 5.3)	2 (0 to 6)	0.923‡
Change (Δ)	0.0 (-1.0 to 0.3)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.3)	0.676‡
KPS				
Pre	85 (70 to 100)*	90 (88 to 100)*	90 (78 to 100)*	0.199‡
Post	80 (68 to 90)	75 (70 to 100)	80 (60 to 100)	0.592‡
Change (Δ)	-10 (-20 to 0)	0 (-20 to 0)	-5 (-20 to 0)	0.903†
Mucositis				
Pre	2 (6.7)†	0 (0.0)†	2 (6.7)†	0.351¶

Variable	CG (n=30)	THEG (n=30)	HEG (n=30)	*p*
Post	12 (40.0)	20 (66.7)	15 (50.0)	0.113¶
Change (Δ)	10 (33.3)[a]	20 (66.7)[b]	13 (43.3)[ab]	0.030¶
VAS				
Pre	1 (0 to 5)	1.5 (0 to 5)†	2 (0 to 5.3)†	0.699†
Post	2 (0 to 5.3)	5.5 (0.8 to 8)	5 (0 to 8)	0.077†
Change (Δ)	0.0 (-1.3 to 3.0)	2.0 (0 – 5.3)	0.5 (0.0 to 4.0)	0.090†

CG, control group; HEG, Hiperboloide exercise group; THEG, TheraBite-Hiperboloide exercise group; RLE: right lateral excursion; LLE: left lateral excursion; KPS: Karnofsky Performance Status; VAS: visual analog scale of pain

* Significant within-group reduction at the 5% level;

† Significant within-group increase at the 5% level;

‡ Kruskal–Wallis test;

§ Analysis of variance (ANOVA);

¶ Pearson's chi-square test.

[a,b] Same superscript letter denotes absence of significant difference on adjusted residuals analysis at the 5% level.

FIGURE LEGENDS

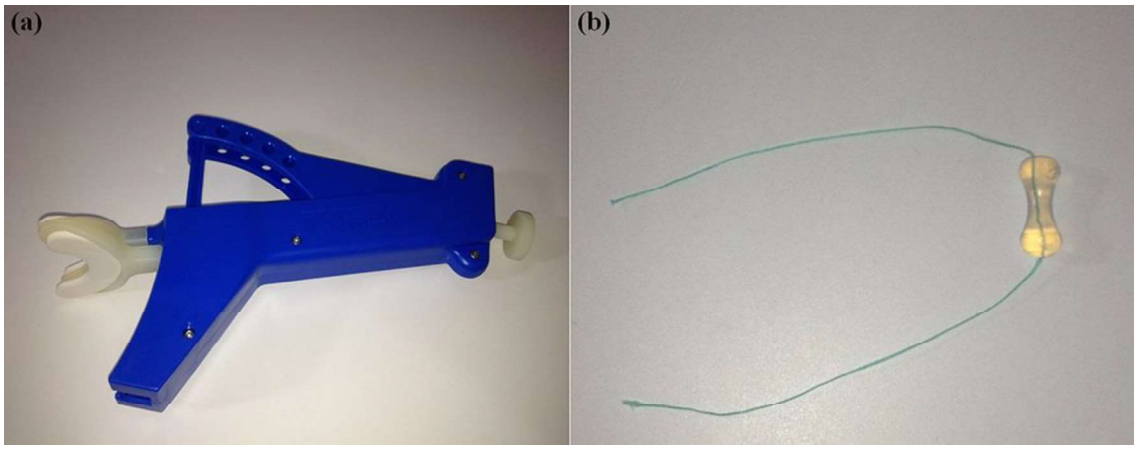
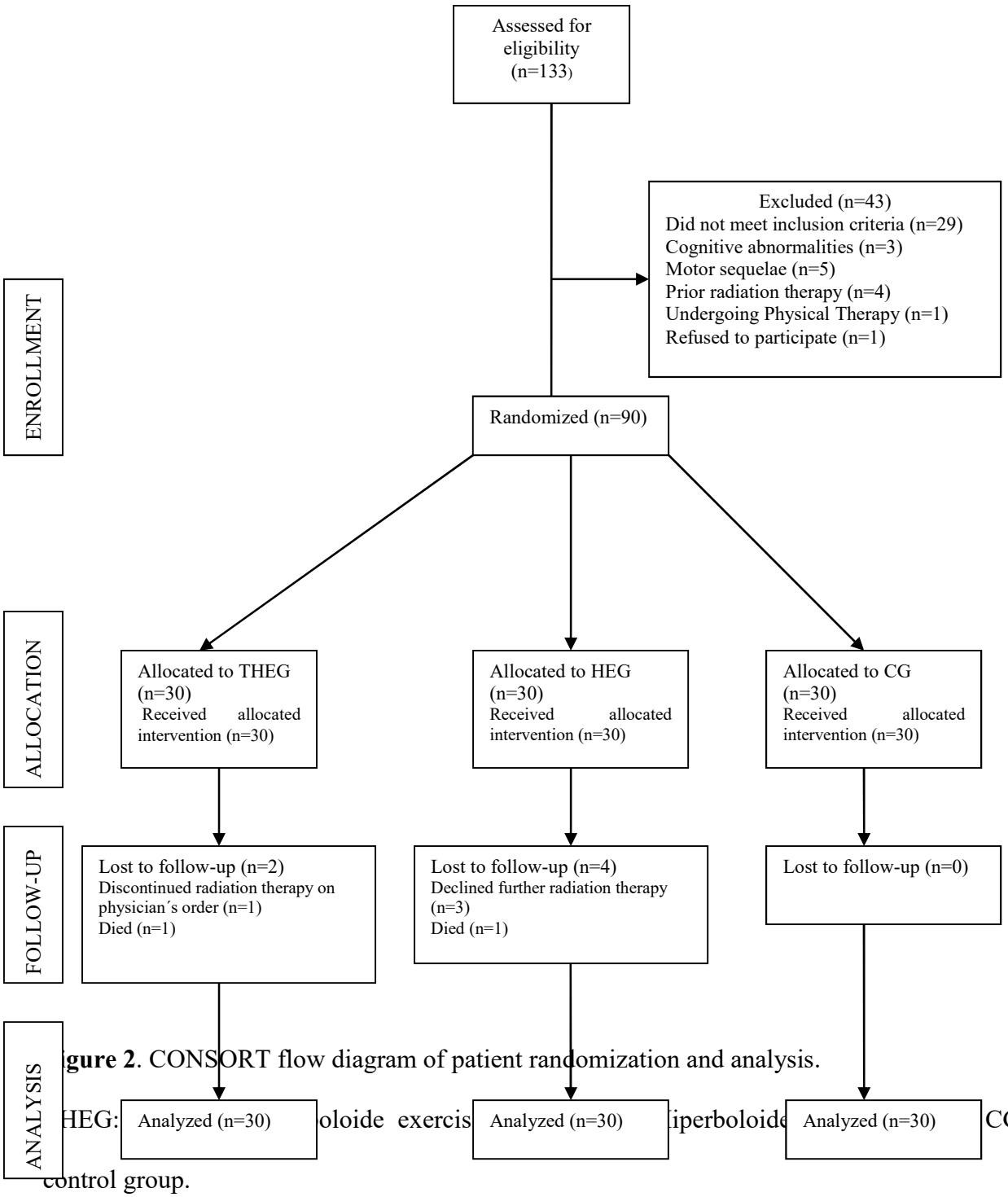


Figure 1. Jaw exercise devices.



igure 2. CONSORT flow diagram of patient randomization and analysis.

HEG: oloide exercis iperboloide CG: control group.

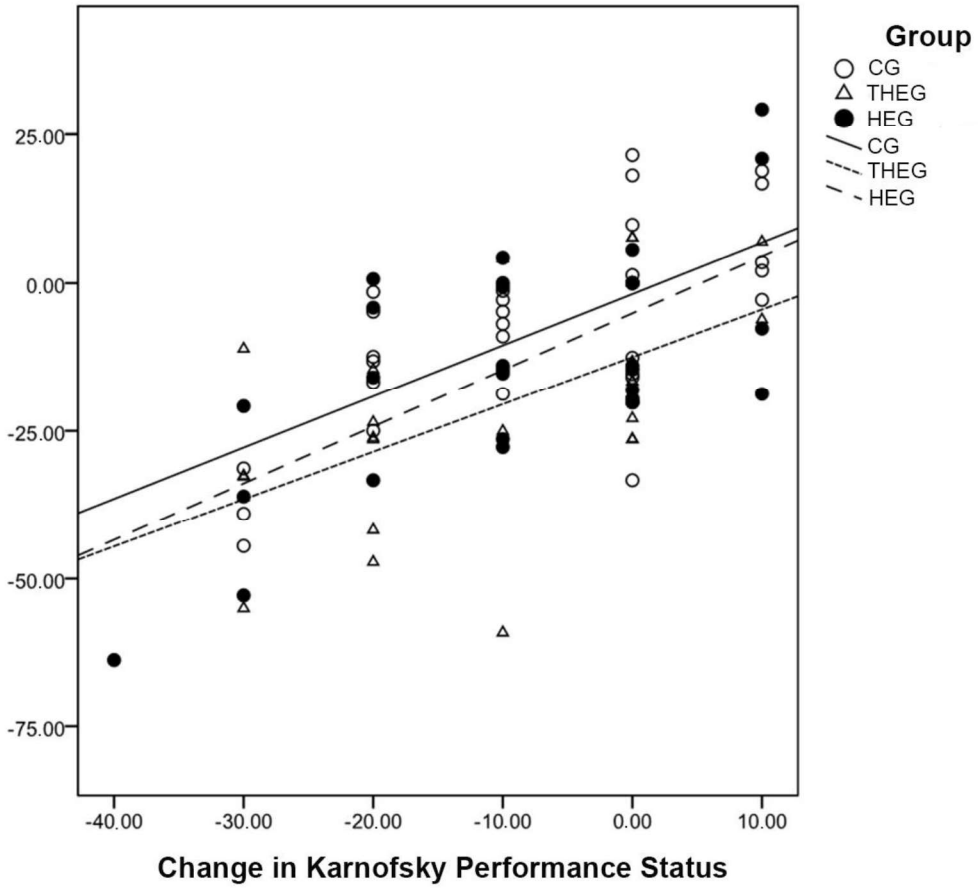


Figure 3. Association between KPS and UW-QOL as determined by Spearman correlation coefficient (r_s).

All groups exhibited a significant association (CG: r_s=0.598, p<0.001; THEG: r_s=0.620, p<0.001; HEG: r_s=0.500, p=0.005).

THEG: TheraBite-Hiperboloide exercise group; HEG: Hiperboloide exercise group; CG: control group

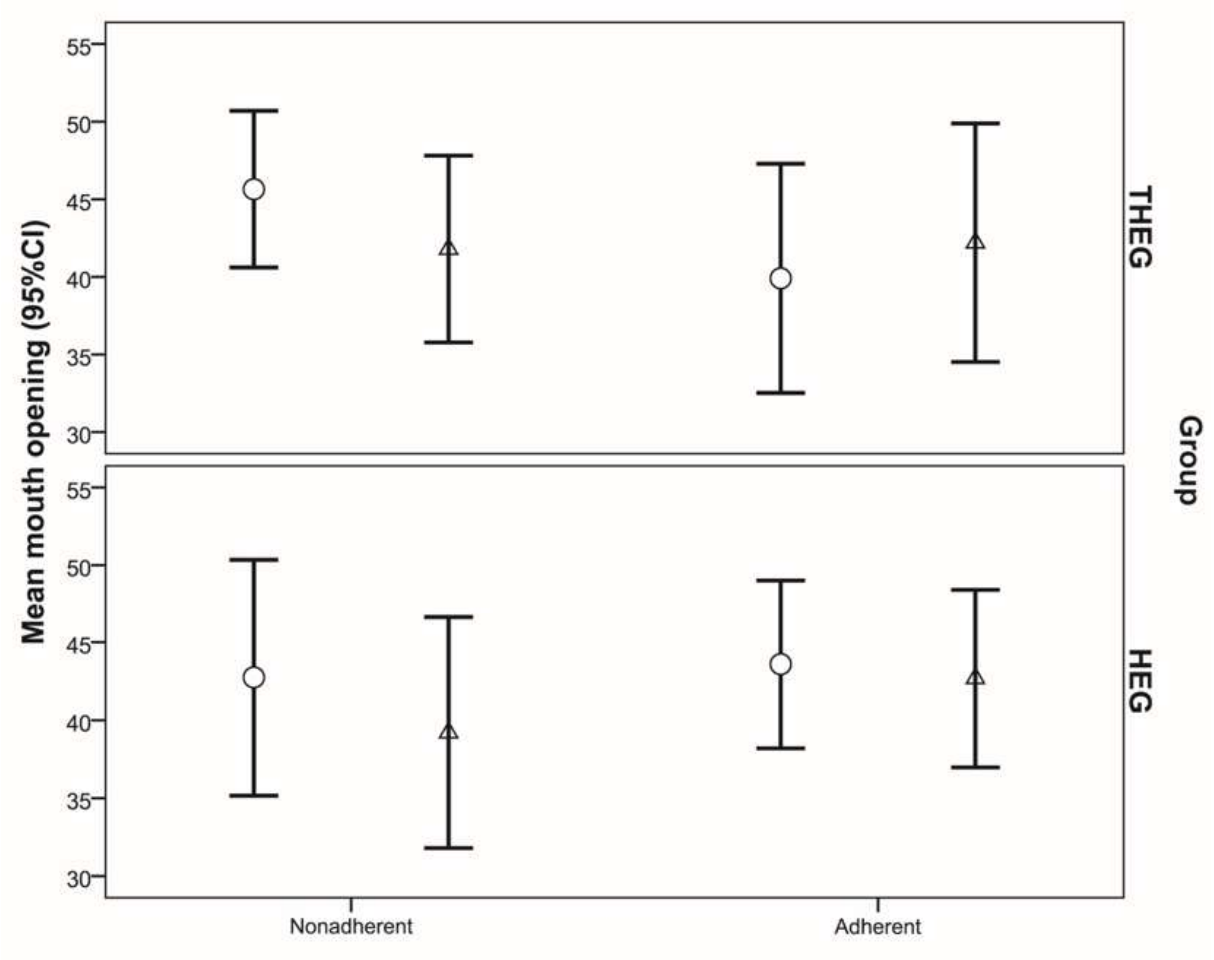


Figure 4. Association between mouth opening and treatment adherence in the TheraBite-Hiperboloide exercise group (THEG) and Hiperboloide exercise group (HEG).

Circles denote the pretreatment mean, and triangles, the post-treatment mean. Whiskers denote the upper and lower limits of the 95% confidence interval.

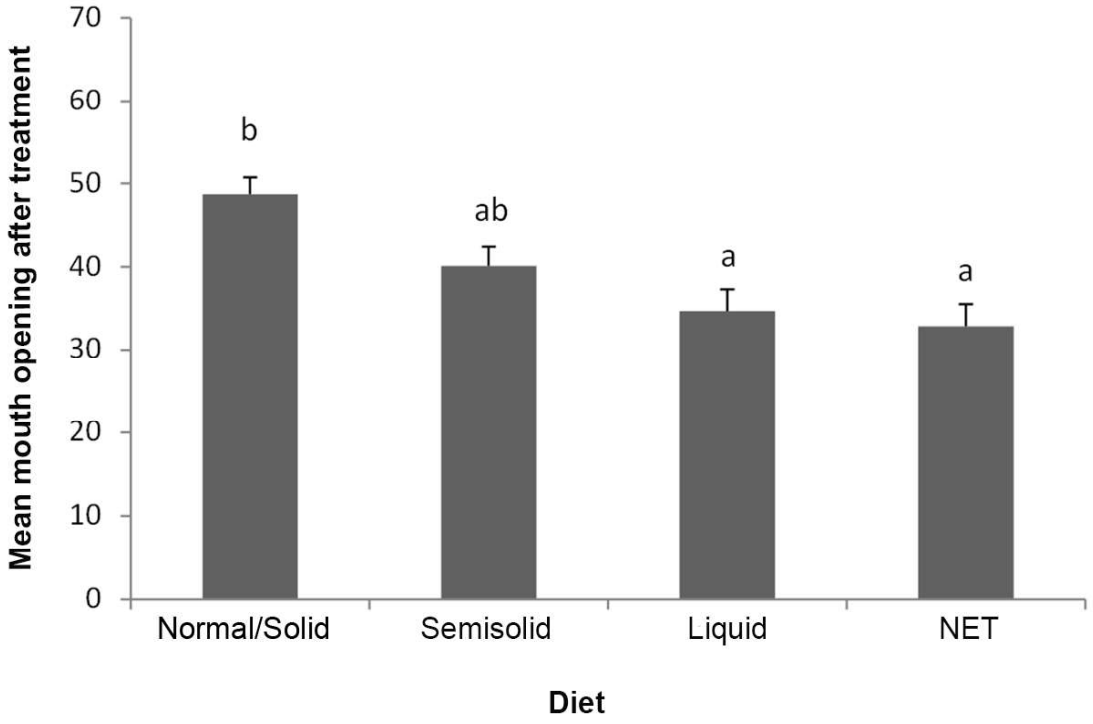


Figure 5. Association between post-treatment mouth opening and type of diet. NET, nasoenteric tube.

a,b Same lowercase letter denotes absence of significant difference at the 5% level (Bonferroni's test).

6 CONCLUSÃO

Com os resultados obtidos no estudo pode-se concluir que os exercícios de fisioterapia minimizam as perdas da medida de abertura bucal nos pacientes irradiados com câncer de cabeça e pescoço.

Quando comparados os valores de AB entre os grupos intervenção, houve uma tendência, porém sem significância estatística, do grupo que utilizou o TheraBite e o Hiperbolóide conjuntamente (GETH) ter menor redução da medida de AB. O grupo que não realizou exercícios (GC) reduziu significativamente a medida da AB.

A capacidade funcional, mensurada pela KPS, reduziu em todos os grupos, demonstrando que não pôde ser alterada pelos protocolos de exercícios profiláticos para trismo.

A qualidade de vida, mensurada pelo UW-QOL, também não pode ser beneficiada pelos protocolos de exercícios profiláticos para trismo, reduzindo em todos os grupos.

Quanto as variáveis demográficas e clínicas, os pacientes que realizaram cirurgia, possuíam tumores em cavidade oral e orofaringe, modificaram a consitência da alimentação e apresentaram mucosite demonstraram maior redução na medida de AB. O grau de mucosite foi um fator independente associado a AB. Quanto maior o grau de mucosite, menor a AB.

A adesão aos protocolos de exercícios foi semelhante nos dois grupos, sendo que nos pacientes do GETH que aderiram ao tratamento foi observado um aumento significativo da medida de AB, o que não pôde ser observado no GEH. A variável grupo também manteve-se associada com a variação da AB após a análise multivariada. O GETH apresenta uma variação menor da AB.

7 ANEXOS

7.1 APROVAÇÃO DO COMITÊ DE ETICA EM PESQUISA DA ISCMPA

IRMANDADE DA SANTA CASA DE MISERICORDIA DE PORTO ALEGRE - ISCMPA

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Fisioterapia Profilática ao Desenvolvimento do Trismo Radioinduzido em Pacientes com Câncer de Cabeça e Pescoço

Pesquisador: Geraldo Pereira Jotz

Área Temática:

Versão: 3

CAAE: 11738213.0.0000.5335

Instituição Proponente: Irmandade da Santa Casa de Misericordia de Porto Alegre - ISCMPA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 259.691

Data da Relatoria: 17/04/2013

Apresentação do Projeto:

Trata-se de um ensaio clínico randomizado e controlado. A randomização será realizada no programa PEPI (Programs for Epidemiologists), subprograma RANDOM, para realização do sorteio dos números aleatórios em cada grupo. O sigilo da alocação será garantido por uma lista de randomização que ficará em um lugar remoto. A seqüência dos números a ser utilizada para randomização será mantida em sigilo ate o momento exato do inicio da intervenção. O avaliador estará cegado quanto ao protocolo de exercícios que o paciente estará realizando, apenas coletará os dados sem saber a qual grupo o paciente pertence. Um pesquisador Colaborador entregará e explicará ao paciente o seu devido protocolo conforme a randomização.A coleta será realizada sempre pelo mesmo avaliador, o qual realizará duas avaliações com o paciente,sendo a primeira antes do início do tratamento radioterápico preferencialmente no dia em que o paciente realizar a simulação (momento 0 ¿ M0) e a segunda imediatamente após a última sessão de radioterapia (momento 1 ¿ M1) . Para isso, todos os pacientes serão submetidos a uma breve anamnese, individualmente, nas dependências do Serviço de Radioterapia do HSR. Dados como sítio tumoral, tipo histológico neoplásico,estadiamento do tumor, campo de radiação, dosagem por sessão de radioterapia, se exposição uni ou bilateral. Serão aplicados exercícios e question de tratamento (curativo ou paliativo) serão coletados do prontuário do paciente. Amostra de 66 pacientes, 3 grupos, GEA, GEB, GEC. Serão aplicados exercícios e questionário.

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UF: RS **Município:** PORTO ALEGRE
Telefone: 5132-1485 **Fax:** 5132-1485 **E-mail:** cep@santacasa.tche.br

IRMANDADE DA SANTA CASA DE MISERICORDIA DE PORTO ALEGRE - ISCMPA

Objetivo da Pesquisa:

Objetivo Primário:

Verificar o efeito de dois protocolos de exercícios fisioterapêuticos na manutenção e/ou ganho da amplitude de movimento mandibular de pacientes com câncer de boca, de faringe, ou ambos em tratamento radioterápico.

Objetivo Secundário:

Comparar os valores de abertura, protusão e excursões laterais da mandíbula obtidos no pré e pós-RT entre os grupos intervenção; Comparar os valores de abertura, protusão e excursões laterais da mandíbula obtidos no pré e pós-RT entre os grupos intervenção e o grupo controle; Comparar os valores de abertura,protusão e excursões laterais da mandíbula obtidos no pré e pós-RT em cada grupo; Comparar os valores de capacidade

funcional obtidos no pré e pós RT entre os três grupos; Analisar qual o domínio do questionário de qualidade de vida foi mais acometido em cada grupo; Verificar se existe correlação entre abertura bucal e qualidade de vida; Verificar se existe correlação entre abertura bucal e capacidade funcional.

Avaliação dos Riscos e Benefícios:

Riscos:

Os procedimentos propostos envolvem um risco considerado mínimo de sentir desconforto na musculatura mastigatória ou na articulação temporomandibular durante a realização do exame físico e/ou do protocolo de xercícios. Essa pesquisa não traz riscos para saúde.

Benefícios:

Benefícios prováveis promover melhora na fala, na aparência facial, na mastigação e na ingestão de alimentos, possibilitar o uso de próteses dentária, facilitar a higienização oral, melhorando o convívio social e a qualidade de vida dos pacientes.

Comentários e Considerações sobre a Pesquisa:

Trata-se de um estudo de relevancia com possíveis melhorias para o convívio social e a qualidade de vida dos pacientes.

Considerações sobre os Termos de apresentação obrigatória:

Apresenta os termos exigidos pela RDC 196/96.

Recomendações:

Não se aplica.

Conclusões ou Pendências e Lista de Inadequações:

Após a reanálise do projeto acima descrito recomenda-se aprovar. A pesquisa atende as exigências, em seus aspectos éticos e metodológicos, as Diretrizes e Normas, especialmente as

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IRMANDADE DA SANTA CASA DE MISERICORDIA DE PORTO ALEGRE - ISCMPA

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Resoluções 196/96, 251/97, 292/99, 346/05, 347/05 do Conselho Nacional de Saúde.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

Após reavaliação do protocolo acima descrito, o presente comitê não encontrou óbices quanto ao desenvolvimento do estudo em nossa Instituição e poderá ser iniciado a partir da data deste parecer.

Obs.: 1 - O pesquisador responsável deve encaminhar à este CEP, Relatórios de Andamento dos Projetos desenvolvidos na ISCMPA. Relatórios Parciais (pesquisas com duração superior à 6 meses), Relatórios Finais (ao término da pesquisa) e os Resultados Obtidos (cópia da publicação).

2 - Para o início do projeto de pesquisa, o investigador deverá apresentar a chefia do serviço (onde será realizada a pesquisa), o Parecer Consubstanciado de aprovação do protocolo pelo Comitê de Ética.

PORTO ALEGRE, 30 de Abril de 2013

Assinador por:
Claudio Teloken
(Coordenador)

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7.2 APROVAÇÃO DO COMITÊ DE ÉTICA EM PESQUISA DA UFCSPA

UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

Elaborado pela Instituição Coparticipante

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Fisioterapia Profilática ao Desenvolvimento do Trismo Radioinduzido em Pacientes com Câncer de Cabeça e Pescoço

Pesquisador: Geraldo Pereira Jotz

Área Temática:

Versão: 3

CAAE: 11738213.0.0000.5335

Instituição Proponente: Irmandade da Santa Casa de Misericordia de Porto Alegre - ISCMPA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 311.888

Data da Relatoria: 20/06/2013

Apresentação do Projeto:

Trata-se de um trabalho de mestrado no PG em Ciências da Saúde sobre o efeito de dois protocolos de exercícios fisioterapêuticos na manutenção e/ou ganho da amplitude de movimento mandibular de pacientes com câncer de boca, de faringe ou ambos, em tratamento radioterápico. Será realizado um exame físico, um questionário de qualidade de vida,

Objetivo da Pesquisa:

Verificar o efeito de dois protocolos de exercícios fisioterapêuticos na manutenção e/ou ganho da amplitude de movimento mandibular de pacientes com de boca, de faringe, ou ambos em tratamento radioterápico.

Avaliação dos Riscos e Benefícios:

Riscos: Os procedimentos propostos envolvem um risco considerado mínimo de sentir desconforto na musculatura mastigatória ou na articulação temporomandibular durante a realização do exame físico e/ou do protocolo de exercícios. Essa pesquisa não traz riscos para saúde.

Benefícios: Melhora na fala, na aparência facial, na mastigação e na ingestão de alimentos, possibilitar o uso de próteses dentária, facilitar a higienização oral, melhorando o convívio social e a qualidade de vida dos pacientes.

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Telefone: (513)303 -8804 **E-mail:** cep@ufcspa.edu.br

UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE

Plataforma Brasil

Continuação do Parecer: 311.888

Comentários e Considerações sobre a Pesquisa:

O projeto está embasado devidamente e os resultados poderão trazer benefícios aos pacientes que realizam radioterapia de cabeça/pescoço e que desenvolvem trismo. As considerações éticas foram atendidas devidamente. Este projeto foi avaliado pelo CEP/ISCMPA parecer nº243.181 de 05/04/2013 apresentou pendências e as respostas foram dadas em 15/04/2013, sendo que o parecer nº 259.691 de 17/04/2013 foi recomendada a aprovação do projeto para início de sua execução no ISCMPA.

Considerações sobre os Termos de apresentação obrigatória:

Apresenta: Folha de rosto com assinatura do responsável na instituição proponente. Folha de encaminhamento CEP UFCSPA, projeto de pesquisa, TCLE, Termo de anuência do responsável pelo setor/instituição onde será realizada a pesquisa; Termo de compromisso para entrega de relatório semestral ou final; Lattes da equipe; demais documentos requeridos pelo CEP ISCMPA.

Recomendações:

Conclusões ou Pendências e Lista de Inadequações:

O projeto atende às exigências em seus aspectos éticos e metodológicos.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

PORTO ALEGRE, 21 de Junho de 2013

Assinador por:
José Geraldo Vernet Taborda
(Coordenador)

Júlia S. Pereira Lima
Vice-Coordenadora CEP/UFCSPA

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Telefone: (513)303 -8804 **E-mail:** cep@ufcspa.edu.br

7.3 REGISTRO *"Clinical Trials"*

A service of the U.S. National Institutes of Health

Physiotherapy for Radiation-induced Trismus

This study is currently recruiting participants. (see **Contacts and Locations**)

Verified March 2014 by *Federal University of Health Science of Porto Alegre*

Sponsor:
Federal University of Health Science of Porto Alegre

Collaborator:
Irmandade Santa Casa de Misericórdia de Porto Alegre

Information provided by (Responsible Party):
Karoline Camargo Bragante, Federal University of Health Science of Porto Alegre

ClinicalTrials.gov Identifier:
NCT02094690

First received: July 12, 2013
Last updated: March 20, 2014
Last verified: March 2014
History of Changes

Full Text View **Tabular View** **No Study Results Posted** Disclaimer How to Read a Study Record

Purpose

The purpose of this study is to assess the effect of two protocols of physiotherapeutic exercises in the maintenance and/or increase of the mandibular range of movement in patients suffering from head and neck cancer (HNC) who are undergoing radiotherapy.

Condition	Intervention
Trismus Radiation-induced Fibrosis	Device: Therabite Device: Hyperboloid

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Factorial Assignment
Masking: Double Blind
(Investigator, Outcomes Assessor)
Primary Purpose: Prevention

Official Title: Prophylactic Physiotherapy Development Of Radiation-Induced Trismus In Patients With Head And Neck Cancer: Randomized
Controlled Clinical Trial

Resource links provided by NLM:

MedlinePlus related topics: Head and Neck Cancer

U.S. FDA Resources

Further study details as provided by Federal University of Health Science of Porto Alegre:

Primary Outcome Measures:

- mouth opening in millimeters (mm) [Time Frame: baseline (before radiotherapy) and post radiotherapy (after the end of radiotherapy). It is expected that the total duration of radiation will vary between a 45 to 60 days.] [Designated as safety issue: No]

  Mouth opening will be assessed before (baseline) and after total radiotherapy treatment (post radiotherapy) in order to establish if there have been any changes resulting from radiotherapy. The measure of mouth opening will be conducted with a pachymeter placed at the incisal edge of the superior and inferior incisor teeth. The maximal vertical distance, in millimeters, between the superior and inferior incisor teeth will be considered the total mouth opening of the patient.

Estimated Enrollment: 69
Study Start Date: June 2013
Estimated Study Completion Date: July 2014
Estimated Primary Completion Date: May 2014 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Active Comparator: Device Hyperboloid 5 min of bilateral mastication alternated with the device hyperboloid The exercises should begin one day before the onset of Radiotherapy (RT) and kept until the end of RT. Repeated 4x a day (after breakfast, lunch, dinner and before going to bed).	Device: Hyperboloid 5 min of bilateral mastication alternated with hyperboloid. The exercises should begin one day before the onset of Radiotherapy and kept until the end of RT. Repeated 4x a day (after breakfast, lunch, dinner and before going to bed).
Active Comparator: Device Therabite • 10 repetitions holding the device Therabite for 30 seconds • 5 min of bilateral mastication alternated with the device hyperboloid The exercises should begin one day before the onset of Radiotherapy and kept until the end of RT. Repeated 4x a day (after breakfast, lunch, dinner and before going to bed).	Device: Therabite 10 repetitions holding Therabite for 30 seconds. The exercises should begin one day before the onset of Radiotherapy and kept until the end of RT. Repeated 4x a day (after breakfast, lunch, dinner and before going to bed). Device: Hyperboloid 5 min of bilateral mastication alternated with hyperboloid. The exercises should begin one day before the onset of Radiotherapy and kept until the end of RT. Repeated 4x a day (after breakfast, lunch, dinner and before going to bed).

No Intervention: Control The control group (GEC) will not receive any of the protocols tested in the study, but together with the other groups, will receive the regular treatment offered by the institution, which is made up of guidance and advice given by the hospital´s nursing team about the radiotherapy treatment. Currently, patients do not receive any information as far as trismus is concerned.	

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria
Inclusion Criteria:

- signature of the Informed Consent Form;
- both male and female individuals, aged 18 or over;
- patients with a diagnosis of anatomopathological mouth and/or pharyngeal cancer;
- patients who have undergone radiotherapy only, or radiotherapy combined with surgery and/or chemotherapy;
- patients who have one or more muscles of mastication in the radiation field, and;
- patients who have scored more than 60% in the

Karnofsky Performance Status. Exclusion Criteria:

- those with facial paralysis, trigeminal neuralgia and/or herpes zoster;
- patients undergoing brachytherapy;
- patients undergoing physiotherapy intervention.

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see LearnAboutClinicalStudies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT02094690

Contacts

Contact: Geraldo P. Jotz, M.D. P.h.d. +55 51 3337 6566 geraldo.jotz@terra.com.br

Locations

Brazil

Hospital Santa Rita - Santa Casa de Porto Alegre **Recruiting**
Porto Alegre, Rio Grande do Sul, Brazil, 90.020-090
Sub-Investigator: Karoline C. Bragante, PT

Sponsors and Collaborators

Federal University of Health Science of Porto Alegre

Irmandade Santa Casa de Misericórdia de Porto Alegre

Investigators

Study Director: Geraldo P. Jotz, Ph.D Federal University of Rio Grande do Sul - UFRGS

More Information

No publications provided

Responsible Party: Karoline Camargo Bragante, PT, Federal University of Health Science of Porto Alegre
ClinicalTrials.gov Identifier: NCT02094690 History of Changes
Other Study ID Numbers: 259.691
Study First Received: July 12, 2013
Last Updated: March 20, 2014
Health Authority: Brazil: Ethics Committee

7.4 NORMAS DE PUBLICAÇÃO *"Head & Neck"*

Author Guidelines

NIH Public Access Mandate

For those interested in the Wiley-Blackwell policy on the NIH Public Access Mandate, please visit our policy statement

For additional tools visit Author Resources - an enhanced suite of online tools for Wiley InterScience journal authors, featuring Article Tracking, E-mail Publication Alerts and Customized Research Tools.

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•Wiley's Journal Styles and EndNote
•Authorship Disclosure Form
•The National Institutes of Health Public Access Initiative

Author Guidelines

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Style

Sources. Webster's Third New International Dictionary (Springfield, MA: Merriam-Webster, Inc) should be used for spelling and hyphenation of nonmedical terms, and Dorland's Illustrated Medical Dictionary , 27th ed (Philadelphia: WB Saunders) for medical terms. The author is directed to the American Medical Association Manual of Style , 8th ed, for general style. Measure (length, height, weight, and volume) should be reported in units or their decimal multiples. Temperature should be given in degrees Celsius, and blood pressure should be given in millimeters of mercury. All hematologic and clinical chemistry measurements should be reported in the metric system in SI (international system) units.

Numbers. Use numerals for all units of measure and time. Spell out the numbers one through nine only for general usage (eg, "We considered only two possibilities.") Spell out numbers beginning a sentence.

Abbreviations. Use only standard abbreviations. Avoid abbreviations in the title. The full term for which an abbreviation stands should precede its first mention in the text. Only standard abbreviations as listed in the AMA Manual of Style should be used without definition.

Manuscript Preparation

Title Page. The title page should include (1) a concise and informative title of the article using terms that can be readily indexed; (2) the authors' full names (first name, middle initial, surname) with highest earned degrees; (3) affiliations for each author (department, section, institution, city and state or country where the work was done); (4) acknowledgment of grant support and of individuals who were of direct help in the preparation of the study; (5) identification of meetings at which the manuscript was presented, if appropriate; (6) the name, address, telephone number, and email address of the author to whom correspondence and/or reprint requests are to be sent; (7) a brief running title; and (8) five key words for indexing.

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King VM, Armstrong DM, Apps R, Trott JR. Numerical aspects of pontine, lateral reticular, and inferior olivary projections to two paravermal cortical zones of the cat cerebellum. J Comp Neurol 1998;390:537-551.

Book

Voet D, Voet JG. Biochemistry. New York: John Wiley & Sons; 1990. 1223 p.

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7.5 PUBLICAÇÃO REFERENTE A ESTA TEMÁTICA

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Evaluation of acute radiation effects on mandibular movements of patients with head and neck cancer

Avaliação dos efeitos agudos da radioterapia sobre os movimentos mandibulares de pacientes com câncer de cabeça e pescoço

Karoline C. Bragante[1], Daniela M. Nascimento[1], Neiro W. Motta[2]

Abstract

Objectives: To evaluate radiotherapy effects (RT) on mandibular movements of patients with head and neck cancer (H&NC) and associate them to the variables: functional capacity, radiation field, disease staging, type of feeding, concomitant chemotherapy and total dose of RT. **Methods:** Twenty-six patients with H&NC were followed up at the RT service. Physical examination was performed in 3 follow up time points: before the beginning of RT (T0), between 14th and 17th session of RT (T1) and after the last session of RT (T2). The physical examination consisted of the assessment of the following variables: mouth opening without pain (MO), maximum mouth opening (MMO), right lateral excursion (RLE), left lateral excursion (LLE) and protrusion (PR) of the jaw. The feeding type and the Karnofsky Performance Status Scale (KPS) were evaluated in each follow up time point. Data with regards to the tumor lesion and the RT were collected from the patient's clinical notes. **Results:** There was a statistical significant reduction in the values of MO (p=0.006), MMO (p=0.001), LLE (p=0.006) and KPS (p=0.001). There was significant a statistical association among the reduction in KPS and decreased measure of MO (r=0.390, p=0.048) and MMO (r=0.435, p=0.026). The mouth and oropharynx radiation fields when combined showed a significant reduction for both the measure of MO (p=0.005) and for MMO (p=0.004). Patients who used nasoenteric tube feeding (NTF) had greater reduction in the measurement of MMO (p=0.031). The remaining variables showed no statistically significant difference. **Conclusion:** Patients with H&NC present reduction of the measures of MO and MMO during the RT, especially if they present reduced functional capacity, have radiation in the mouth and oropharynx fields and used NTF.

Keywords: radiotherapy; trismus; head and neck neoplasms; joint range of motion.

Resumo

Objetivos: Avaliar os efeitos da radioterapia (RT) sobre os movimentos mandibulares de pacientes com câncer de cabeça e pescoço (CCeP) e associá-los às variáveis: capacidade funcional, campo de radiação, estadiamento da doença, tipo de alimentação, quimioterapia concomitante e dose total de RT. **Métodos:** Vinte e seis pacientes com CCeP foram acompanhados em um serviço de RT. O exame físico ocorreu em três momentos: antes do início da RT (M0), entre a 14ª e 17ª sessão (M1) e após a última sessão de RT (M2) para verificação de variáveis, como: abertura bucal sem dor (AB), abertura bucal máxima (ABm), excursão lateral direita (EXd), excursão lateral esquerda (EXe) e protrusão (PR) da mandíbula. O tipo de alimentação e a Escala de Karnofsky (EK) foram reavaliados em cada momento. Dados a respeito da lesão tumoral e RT foram coletados do prontuário do paciente. **Resultados:** Houve redução significativa nos valores de AB (p=0,006), ABm (p=0,001), EXe (p=0,006) e EK (p=0,001). Houve associação estatisticamente significativa entre a redução na EK e a diminuição de AB (r=0,390; p=0,048) e de ABm (r=0,435; p=0,026). Os campos de radiação da boca e orofaringe, quando agrupados, apresentaram redução significativa tanto para a medida de AB (p=0,005) quanto para ABm (p=0,004). Os pacientes que utilizaram sonda nasoentérica (SNE) apresentaram maior redução da medida de ABm (p=0,031). As demais variáveis não apresentaram diferença estatisticamente significativa. **Conclusão:** Os pacientes com CCeP apresentam redução das medidas de AB e ABm no decorrer da RT, principalmente se apresentarem redução da capacidade funcional, tiverem irradiação para os campos da boca e orofaringe e fizerem uso de SNE.

Palavras-chave: radioterapia; trismo; neoplasias de cabeça e pescoço; amplitude de movimento articular.

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Introduction

Head and neck cancer (H&NC) presents a worldwide estimated incidence of 780.000 new cases per year[1]. In Brazil, the National Institute of Cancer (INCA) estimated that in 2010 10.330 new cases of cancer involving the head and neck areas among men and 3.790 among women occurred[2]. The anatomical sites that are included in this group of neoplasms are the oral cavity, which comprises oral mucosa, lips, gums, hard palate, tongue, mouth floor and retromolar trigone; pharynx, which includes oropharynx (base of tongue and soft palate), nasopharynx and hypopharynx (pyriform sinus, pharyngeal wall and post-cricoid area); nasal cavity and paranasal sinuses; glottis and supraglottic larynx; and salivary glands[1,3]. Approximately 40% of H&NC occur in the oral cavity, 25% in the larynx, 15% in the pharynx, 7% in the salivary glands and 13% in other areas[3,4]. The most frequent histological type is the squamous cell carcinoma, present in more than 90% of cases[1,3,5].

Several factors are involved in the genesis of head and neck cancer, including genetic predisposition[1,6]; professional activity such as exposure to textile fibers, leather and nickel[7]; social conditions and habits, being the consumption of tobacco and alcohol the most significant risk factors[1,3,8,9]. Variables such as age over 40 years-old, male gender and white race may be also considered as predisposing factors for its development[3].

Therapeutic modalities for the treatment of head and neck cancer include surgical, procedures, radiotherapy and chemotherapy, which may be used separately or in combination[8-10]. Radiotherapy (RT) is a modality used in the treatment of malignant tumors which the therapeutic agent is the ionizing radiation, i.e. that one which promotes ionization in the environment where charged, turning it electrically unstable[11,12]. By creating unstable atoms whose free electrons join to other adjacent atoms, which also become unstable with increased negative charges, damage to the cellular deoxyribonucleic acid (DNA) occurs, preventing the replication of the neoplastic cell[13]. The ionizing radiation treatment, however, is not selective, as it does not have the capacity to differentiate the normal cells from the malignant ones, which turns it toxic for the body[13].

Adverse reactions due to RT depend on the volume and the area that will be irradiated, whether the exposure will be unilateral or bilateral, total dose, dose fractionation, age, patient clinical condition, social habits, such as alcoholism and smoking and the associated treatments[12-15]. Most of patients undergoing RT for head and neck receive a total dose from 50 to 70 Gray (Gy) as a curative dose. These doses are fractionated in a period from five to seven weeks, once a day, five days a week, with daily dose of approximately 2 Gy[8,11,15].

The side effects of RT established for the treatment of patients with H&NC significantly interfere on the quality of life of these individuals[16]. Among the effects located in the head and neck area it may be mentioned: mucositis, dermatitis, dry mouth, hypogeusia, osteoradionecrosis, fibrosis and trismus[4,11,13,15]. Radiation-induced trismus, a reduced mobility of the jaw[17,18] due to the fibrosis that occurs in the masticatory muscles when they are in the radiation field[5,17-19] has a negative impact on the quality of life of the patients[5,19], as it causes alterations in the facial appearance[18], difficulty in food intake[5,10,20], in the use of dental prostheses[10] and in the speech[5], compromises the oral hygiene[5,19] and it may lead to depression[5].

Some authors[9,21] suggest that radiation-induced trismus may only be established months after the end of radiation therapy and if the patient underwent to high doses, while other authors[5,22] state that, during the course of radiation therapy may occur restriction of the mandibular movements even after low doses of irradiation. Several studies[17,21-24] reported the relationship of trismus with specific anatomical structures in the radiation field. In addition, some authors[17,25] confirm the direct influence of this therapy associated with chemotherapy in the emergence of this complication, while other authors[5] disagree.

Due to the contradictory data in the scientific literature with regards to the appearance of radiation-induced trismus in the course of irradiation therapy and the high rate of patients with H&NC undergoing high doses of RT in extensive radiation fields[11], there is a need to better investigate the occurrence of possible changes in the mandibular mobility in irradiated patients, as well as which associated factors would be involved in the onset of these complications, so that after this investigation, data for prevention programs and/or reduction of such dysfunctions may be provided.

Therefore, the objectives of this study were to evaluate the effects of RT on the mandibular movements of patients with H&NC and, secondarily to investigate the association of these effects with the following variables: functional capacity, radiation field, disease staging, type of feeding, use of concomitant chemotherapy and total dose of RT.

Methods

Study design and sample

This is a prospective cohort study in which patients with H&NC, assisted by the Unified Health System in the Radiotherapy Service of the Santa Rita Hospital (HSR) of the Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA), Porto Alegre, RS, Brazil, were evaluated and followed up. These patients started radiotherapy between February and May 2010. The sample size calculation was carried out based on the study

of Grandi et al.[26] for a significance level of 5%, a power of 80% and an effect size of at least 0.6 among the evaluations, and it resulted a minimum number of 22 patients to contemplate the study design.

The assessment of eligibility for participation in the study followed the criteria: 1) inclusion criteria: Male and female over 18 years-old, with diagnosis of H&NC undergoing curative RT alone or in combination with chemotherapy, with one or more masticatory muscles on the radiation field and who had percentile higher than 40% in the Karnofsky Performance Status Scale (KPS)[27]. 2) exclusion criteria: individuals who had performed surgical intervention to remove the tumor in any of the mastication muscles, presenting facial palsy, trigeminal neuralgia or herpes zoster, patients in treatment with brachytherapy, patients who were receiving physical therapy, who have not performed any of the stages of the study and who refused to participate in the study.

Data from 32 patients were collected, being five patients lost to follow-up due to interruption of the radiotherapy as requested by the physician (n=1) and for abandonment of the treatment with irradiation therapy in the above-mentioned institution (n=4). One patient was excluded from the study for not being assessed in the last follow up. This study had a final sample of 26 patients. The data collection was concluded in July 2010.

Data collection

All patients who started the RT in HSR received information, in group, about the treatment by the nursing staff. In these groups, patients who met the inclusion criteria of the study were identified and the informed consent form was presented to them. After signing the consent form the data collection was initiate.

Each patient individually underwent to a brief initial interview and variables such as age, family history of cancer, smoking and alcoholic habits, as well as how long they have being smoking and/or drinking, classification by KPS scale, which is a scale of functional performance used in the prognosis of cancer therapy[27], and type of feeding[28,29] were collected. Data such as tumor location, histological type of tumor, tumor stage[30], associated chemotherapy, radiation field and dose per session of RT were collected from the patient's chart for future correlations and characterization of sample.

The data collection from the physical examination aimed to assess the variables mouth opening without pain (MO), maximum mouth opening (MMO), right lateral excursion (RLE), left lateral excursion (LLE) and protrusion (PR) of the jaw followed the instructions and specifications of the clinical examination of the Protocol of Diagnostic Criteria of Temporomandibular Disorders (RDC/TMD)[31]. The physical examination was always carried out by the same examiner, who was familiarized with this protocol, in three different time points: before the beginning of the RT, time 0 (T0); between 14th and 17th session, time 1 (T1) and immediately after the last session of the RT, time 2 (T2). Variables such as type of feeding and KPS scale were also evaluated at each time points.

All patients were treated with irradiation therapy by photons in parallel pairs or wedge angle with daily dose from 1.8 to 2 Gy until the end of treatment of approximately seven weeks. The total dose of the RT ranged from 50 to 70 Gy.

The present study was approved by the Ethics in Research Committee of the Centro Universitário Metodista do Instituto de Porto Alegre (IPA) (Porto Alegre, RS, Brazil, number 393/2009), and by the Ethics in Research Committee of the ISCMPA, protocol 031/10.

Statistical Analysis

The collected data were stored in the *Microsoft Excel 2003*. To characterize the sample, the categorical variables of this study were described through absolute and relative frequencies; the continuous variables, through means and standard deviations for those that presented a normal distribution, and median and interquartile ranges in case of asymmetric distribution variables. The Shapiro-Wilk test was used to verify the normality of data. The comparison between physical examination variables in the three different time points was verified by the ANOVA for repeated measures followed by Bonferroni test or, when appropriate, by its correspondent non-parametric Friedman test followed by Wilcoxon test. The comparison among the physical examination variables and disease stage, type of feeding and radiation field was obtained by the one-way ANOVA test followed by Tukey test, and the variable chemotherapy was compared with the variables of physical examination by the Student *t* test. Correlations were performed through Pearson correlation test. The statistical program used was SPSS, version 17.0. The significance level was set at α=0.05 for all statistical analyses.

Results

In relation to the variable gender, all 26 (100%) participants of this study were male. The volunteers' age ranged between 45 and 74 years old, with a mean age of 59.0 (SD=8.8) years. Regarding the distribution by race, there were 20 (76.9%) Caucasians, five (19.2%) Afrocaucasian and one (3.9%) melanoderm. Regarding social habits, 26 (100%) were smokers, with smoking mean time duration of 37.4 (SD=12.7) years, and 19 (73.1%)

participants reported regular intake of alcohol, with mean time duration of 29.5 (SD=13.0) years. With regards to the family history of cancer, 13 (50%) have reported family history of cancer and 13 (50%) were not sure or had no cases of cancer in the family. Patients' distribution according to the tumor location, tumor histological type and tumor stage is shown in Table 1.

Regarding the comparison of the variables of the physical examinaton in the three different time points, there was a statistically significant reduction on the values of MO, MMO and LLE. There was also observed a statistically significant reduction in relation to KPS scale (Table 2).

There was a moderate positive statistically significant correlation among the reduction of the KPS scale and the decreased of MO (r=0.39; p=0.048) and MMO measurements (Figure 1).

The analysis of the radiation fields shows that there was a tendency of the oropharynx and mouth fields present a greater reduction of mouth opening (Table 3). If oropharynx and mouth fields are combined and compared with the other radiation fields, it can be observed a statistically significant reduction in both, MO (p=0.005) and MMO (p=0.004) measurements. There were no statistically significant differences (p>0.05) among tumor staging and both MO and MMO measurements.

With regards to the type of feeding in T0 all patients reported oral food intake being the food in the normal consistency; in T1, seven (26.9%) patients remained with normal feeding; 11 (42.3%) reported eating only food in pasty consistency and eight (30.8%) patients informed feeding exclusively for nasoenteric tube feeding (NTF). In T2, data about the type of feeding were the same as in T1.

Comparison between the variation of MO and MMO measurements according to the type of feeding showed values significantly lower of MMO measurement in patients who used NTF (Table 4).

Regarding the use of chemotherapy (cisplatin), 13 (50%) participants had used it combined with the RT. When the patients who underwent chemotherapy are compared with those who did not realize this therapy there was no statistically significant difference (p>0.05) on the variation of MO and MMO measurements.

There was no statistically significant association between the total dose of radiation and the reduction of MO (r=-0.111; p=0.591) and MMO (r=-0.164; p=0.423) measurements.

Table 1. Patients distribution by tumor location, tumor histological type and tumor stage.

Variables	n (%)
Larynx	12 (46.2)
Oropharynx	10 (38.9)
Mouth	8 (30.8)
Hypopharynx	4 (15.4)
Nasopharynx	1 (3.8)
Squamous cell carcinoma	25 (96.2)
Undifferentiated Carcinoma	1 (3.8)
Stage I	1 (3.8)
Stage II	4 (15.4)
Stage III	5 (19.2)
Stage IVA	12 (46.2)
Stage IVB	4 (15.4)

Table 2. Comparison of the variables from the physical examination at three follow up times points.

Variables	T0	T1	T2	p
MO	36.7±10.4[b]	34.2±11.4[a,b]	32.2±9.8[a]	0.006*
MMO	40.9±10.6[b]	38.7±12.1[b]	35.9±10.2[a]	0.001*
RLE	8 (5-10)	8 (4.8-10)	5.5 (3.8-8.5)	0.133**
LLE	9 (6.8-10)[b]	8 (5.0-10)[a]	8 (3-10)[a]	0.006**
PR	5 (2.8-8.3)	4 (2.0-5.0)	4 (2-6.3)	0.154**
KPS	83.1±13.5[b]	75.8±13.3[a]	72.7±14.8[a]	0.001*

The values of MO: Mouth opening; MMO: maximun mouth opening and KPS: Karnofsky Performance Status scale, are expressed in means and standard deviations. The values of RLE: right lateral excursion; LLE: left lateral excursion e PR: protrusion are expressed as medians and interquartile ranges *ANOVA for repeated measurements **Friedman test. [a,b] letters are not significantly different by the Bonferroni test or Wilcoxon p<0.05.

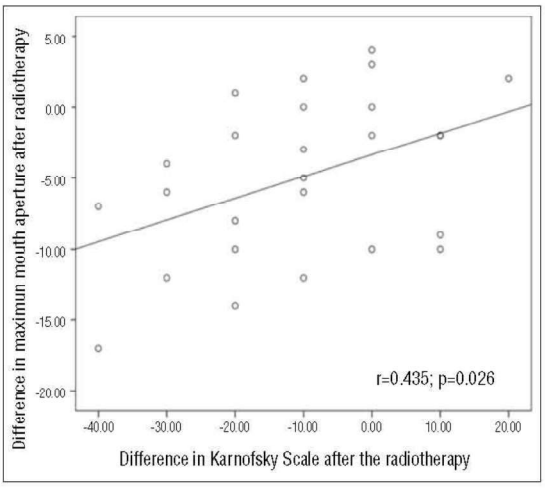

Figure 1. Pearson's correlation.

Table 3. Mouth opening variation according to the radiation field.

Variables	Δ MO=M0-M2	p*	Δ MMO=M0-M2	p*
Oropharynx	-13±4.2		-11.5±7.8	
Larynx	-5.2±7.4	0.059	-5.3±6.3	0.059
Hypopharynx	0.0±0.0		-2.0±0.0	
Mouth	-10.0±4.7		-11.0±1.7	
Drainage areas	-2.1±5.2		-2.8±4.5	

The values of MO: Mouth Opening and MMO: Maximum Mouth Opening are expressed as means and standard deviations. *Anova one-way.

Table 4. Mouth opening variation according to the field of feeding.

Variables	Δ MO=M0-M2	p*	Δ MMO=M0-M2	p*
Normal	-0.6±3.8		-0.6±3.6[b]	
Pasty	-4.2±5.8	0.057	-5.6±5.0[a,b]	0.031
NTF	-8.4±7.4		-7.9±6.2[a]	

The values of MO: Mouth Opening e MMO: Maximun Mouth Opening are expressed as means and standard deviations.*Anova one-way. a,b: same letters do not differ by the Tukey test (p<0.05).

Discussion

In relation to gender, age and race, the present results support the results existent in the literature, which showed a higher incidence of H&NC in males[3,7-9,12,32], with predominance of individuals between the 6th and 7th decade of life[3,4,8,9,33] and Caucasian[3,12,26].

Regarding the social habits all participants of this study declared themselves smokers and 73.1% and consumed alcohol, which strengthens the association between the intake of alcohol and tobacco for the development of H&NC[3,7,9,34]. Half of sample of the present study reported to have family history of cancer indicating that genetic predisposition may also be a risk factor for H&NC as shown in recent studies[1,34-36].

The predominant histological type in this study was the squamous cell carcinoma, which is in agreement with the statistics of INCA[2] and with other studies[3,5,9,26]. With regards to the anatomical site larynx tumor was the most prevalent in this study disagreeing with epidemiological studies that indicate predominance of cancers of the oral cavity[3,4,34]. Such disagreement may be explained due to the previous studies surgical patients were also included and in the present study patients with mouth cancer who require surgical procedures that embrace the masticatory muscles[37] were excluded of the study. In relation to the patients' distribution by tumor staging, 46.2% presented IVA stage. The literature shows high incidence of advanced stage H&NC at the moment of the clinical diagnosis[3].

Our results demonstrate that the RT significantly reduces the measure of MO and MMO over the course of the radiotherapy as reported in the study of Goldstein et al.[22]. Some authors, however, obtained different results, finding the presence of trismus only after nine weeks and six months of the end of the RT[5,21]. These discrepancies in the literature may be related with bias of retrospective data collections and with the variability in the evaluation form and definitions of trismus. Many authors[21,38] have adopted as a measure of trismus a MO lower than 35 mm, while other authors[19,39] have adopted the measure of 40 mm. Another study[5] considered as criterion for trismus a MO lower than 35 mm in dentulous patients and a MO lower than 40 mm in edentulous patient. There is also no consensus on how to evaluate the mouth opening. It can be performed with a millimeter ruler, Will´s compasses or calipers[40].

The present study used a millimeter ruler for the measurements, as recommended by RDC/TMD[31] and had not established a cutoff point for trismus. We consider to be more accurate to evaluate the variation of measurement of the mandibular movements at different time points, thus if there were any restrictions of these movements already (inherent to the individual or due to the tumor) it was identified before the beginning of the RT allowing therefore, that only the alterations in consequence of the irradiation were analyzed. Many patient with head and neck cancer already present before the beginning of RT limited MO due to tumor invasion in the masticatory muscles or due to spasm reflex of these muscles[18,21,41,42]. This symptom tends to relieve or disappear during the course of the irradiation therapy, but it may reappear gradually in case of radiation-induced fibrosis in the masticatory muscles[21].

The LLE measure showed statistically significant reduction. Due to the patients in this study had received radiation therapy in parallel pairs or in angled wedge, this reduction could be attributed to the unequal application of irradiation on parallel fields in patients who received bilateral radiation, as the uneven application on parallel opposed fields results in radiation-induced trismus on the side that received more irradiation according to the study of Wollin, Gilbert and Kagan[43]. Since in the present study the application method of the RT was not controlled and the radiation doses were not calculated for the specific muscle groups, it is not possible to affirm that such outcome is due to uneven application of radiation on parallel fields, being this difference occurring by chance. Prospective studies controlling the application of the RT on parallel fields should be carry out to determine whether the unequal application results in radiation-induced trismus on the side that have received more irradiation.

Technological advances in radiotherapy have been increasing the survival of patients with tumors[15] demonstrating the importance of taking in consideration the impact of RT on functional and cosmetic aspects[44]. Our results demonstrated a significant reduction on the patients' functional status in the middle of the treatment, as have been reported in other study[45]. There was a positive correlation among the reduction in KPS scale and reduction of MO and MMO measurements, i.e. the patients that have presented a greater reduction the MO measurement were the ones who had the worst level of physical performance, which corroborate with the literature[18]. There is a need for a global physical rehabilitation in order to benefit the functionality of oncologic patients.

The region where the tumor is irradiated is known as radiation field. The core of the tumor receives the dose predetermined by the radiotherapist and the surrounding tissues receive lower doses of irradiation[15]. Our results showed that the radiation fields of oropharynx and mouth presented a greater reduction of the MO and MMO measurements. This occurs because in these fields the main jaw elevator muscles (masseter and medial pterygoid)[46] are in the path of the radiation beam receiving higher doses of radiation, which may lead to fibrosis of these muscles and generate radiation-induced trismus, corroborating with the literature[5,17,19,22,42].

In the study of Johnson et al.[18], patients who presented greater MO restriction were the patients with more advanced

disease staging. This finding conflicts with the results of the present study, which demonstrate no statistically significant difference between the variation of the MO and MMO measurements and the tumor stages. According to some studies[1,47], tumors that have the same clinical staging may demonstrate different patterns of evolution, suggesting that adverse reactions of RT require the analysis of other complementary factors.

According to some studies[29,41,48,49] from 50 to 60% of patients with H&NC have a relatively impaired feeding due to factors such as sore throat, dysphagia, xerostomy, ageusia, among others, and a significant involuntary weight loss becoming extremely necessary the enteral feeding tube. In this study, 30.8% of the patients fed through NTF since the middle of radiotherapy, and 42.3% had to change the consistency of food at the same period. Our results demonstrated that patients who fed trough NTF had greater MMO restriction compared to patients who remained feeding orally. The mandibular hypomobility caused by the use of NTF accelerates the degeneration of the muscles and the temporomandibular joint caused by RT[50]. Several studies have reported the use of chewing gum for the treatment of trismus[19,26]. Thus, it may be supposed that the chewing had a preventive function on the MO restriction in patients who remained feeding orally.

In the organ preservation therapy, chemotherapy combined with RT is frequently used nowadays[17]. In this study, half of patients had chemotherapy combined with RT. Researchers report that the combination of these treatments presents greater benefit for the tumor control, on the other hand, it increases the toxicity to the body resulting in excessive side effects[17,29]. In our results, however, chemotherapy combined with RT did not increase the incidence of MO and MMO restrictions, confirming the findings of Louise's Kent et al.[5].

In the present results there was no association between total dose of RT and MO restriction. Individuals who received the same total dose of RT showed different MO pattern, corroborating with some studies[51,52]. Factors as radiation field, patient's functionality and type of feeding showed greater influence on the patient's MO compared to the total dose of radiation in the short-term evaluation of trismus.

Several studies[24,42,53,54] have reported that the prevention of trismus instead of its treatment is the most desirable objective since the radiation-induced trismus is of difficult to recover. Therefore, early intervention of a physiotherapist, who is inserted in the multidisciplinary team working in the care of cancer patient, becomes extremely necessary to prevent or to reduce this frequent complication, with is occasionally ignored but with significant negative impact on the quality of life of patients with H&NC. It is suggested that clinical trials to verify which physical therapeutic exercises would be more effective in the prevention of MO limitation should be carried out.

The main limitation of this study was that, when creating subgroups for analysis of the secondary objectives a type II error might have occurred due to the small sample size. Due to the small sample size, the anatomical subsites of the tumor lesion were not analyzed with regards to the MO restriction, which should be investigated in future researches. Longer follow up period is also necessary for understanding the progression and severity of trismus over time. Prospective cohort study with a longer follow up time is suggested.

Conclusion

The results of this study suggest that patients with H&NC, without physical therapeutic intervention, present restriction of mandibular movements during radiotherapy indicating that this physical complication should be evaluated during the course of RT, mainly if the patients present a reduced functional capacity, have radiation to mouth and oropharynx fields and used of NTF. The variables disease staging, total dose of RT and combined chemotherapy had not represented statistically significant risk factors in relation to the occurrence of mandibular hypomobility.

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