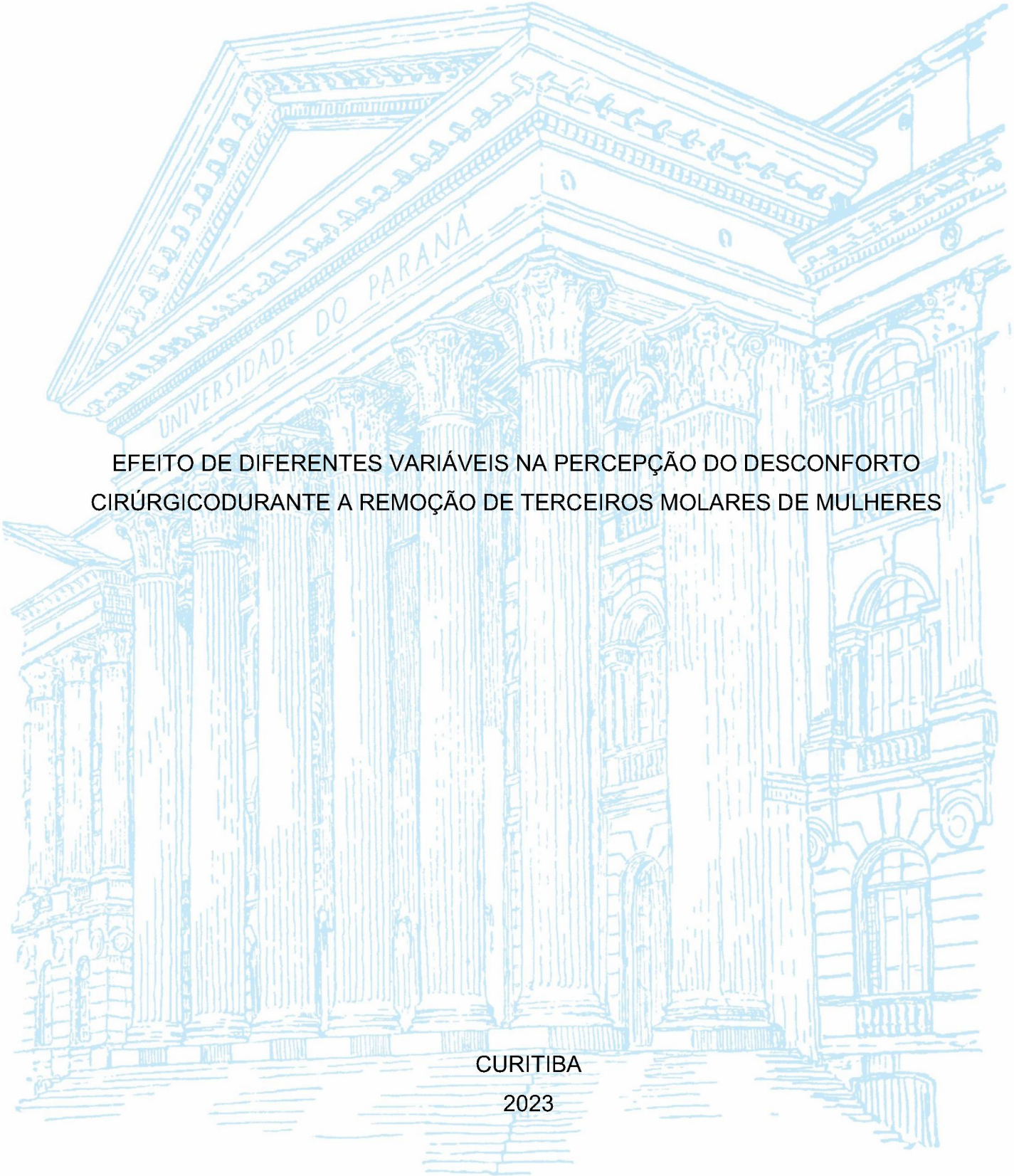
UNIVERSIDADE FEDERAL DO PARANÁ

GISELLE EMILÃINE DA SILVA REIS



EFEITO DE DIFERENTES VARIÁVEIS NA PERCEPÇÃO DO DESCONFORTO CIRÚRGICODURANTE A REMOÇÃO DE TERCEIROS MOLARES DE MULHERES

CURITIBA

2023

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EFEITO DE DIFERENTES VARIÁVEIS NA PERCEPÇÃO DO DESCONFORTO CIRÚRGICO DURANTE A REMOÇÃO DE TERCEIROS MOLARES DE MULHERES

Tese apresentada como requisito parcial à obtenção do título de Doutora, Programa de Pós-graduação em Odontologia, Setor de Ciências da Saúde, Universidade Federal do Paraná.

Orientadora: Profa. Dra. Rafaela Scariot
Coorientador: Prof. Dr. Delson João da Costa

CURITIBA

2023

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Orientador: Profa. Dra. Rafaela Scariot
Coorientador: Prof. Dr. Delson João da Costa

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MINISTÉRIO DA EDUCAÇÃO
SETOR DE CIÊNCIAS DA SAÚDE
UNIVERSIDADE FEDERAL DO PARANÁ
PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
PROGRAMA DE PÓS-GRADUAÇÃO ODONTOLOGIA - 40001016065P8

ATA Nº217

ATA DE SESSÃO PÚBLICA DE DEFESA DE DOUTORADO PARA A OBTENÇÃO DO GRAU DE DOUTORA EM ODONTOLOGIA

No dia trinta de outubro de dois mil e vinte e tres às 08:30 horas, na sala Anfiteatro rosa - banca será hibrida, Odontologia - Jardim Botanico, foram instaladas as atividades pertinentes ao rito de defesa de tese da doutoranda **GISELLE EMILÃINE DA SILVA REIS**, intitulada**: Efeito de diferentes variáveis na percepção do desconforto cirúrgico durante a remoção de terceiros molares de mulheres**, sob orientação da Profa. Dra. RAFAELA SCARIOT. A Banca Examinadora, designada pelo Colegiado do Programa de Pós-Graduação ODONTOLOGIA da Universidade Federal do Paraná, foi constituída pelos seguintes Membros: RAFAELA SCARIOT (UNIVERSIDADE FEDERAL DO PARANÁ), LEONARDO PEREZ FAVERANI (UNIVERSIDADE ESTADUAL PAULISTA, FACULDADE DE ODONTOLOGIA DO CAMPUS DE ARAÇATUBA.), YASMINE MENDES PUPO (UNIVERSIDADE FEDERAL DO PARANÁ), JULIANA FELTRIN DE SOUZA CAPARROZ (UNIVERSIDADE FEDERAL DO PARANÁ). A presidência iniciou os ritos definidos pelo Colegiado do Programa e, após exarados os pareceres dos membros do comitê examinador e da respectiva contra argumentação, ocorreu a leitura do parecer final da banca examinadora, que decidiu pela APROVAÇÃO. Este resultado deverá ser homologado pelo Colegiado do programa, mediante o atendimento de todas as indicações e correções solicitadas pela banca dentro dos prazos regimentais definidos pelo programa. A outorga de título de doutora está condicionada ao atendimento de todos os requisitos e prazos determinados no regimento do Programa de Pós-Graduação. Nada mais havendo a tratar a presidência deu por encerrada a sessão, da qual eu, RAFAELA SCARIOT, lavrei a presente ata, que vai assinada por mim e pelos demais membros da Comissão Examinadora.

CURITIBA, 30 de Outubro de 2023.

Assinatura Eletrônica
31/10/2023 21:33:22.0
RAFAELA SCARIOT
Presidente da Banca Examinadora

Assinatura Eletrônica
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LEONARDO PEREZ FAVERANI
Avaliador Externo (UNIVERSIDADE ESTADUAL PAULISTA, FACULDADE DE ODONTOLOGIA DO CAMPUS DE ARAÇATUBA.)

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YASMINE MENDES PUPO
Avaliador Interno (UNIVERSIDADE FEDERAL DO PARANÁ)

Assinatura Eletrônica
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JULIANA FELTRIN DE SOUZA CAPARROZ
Avaliador Interno (UNIVERSIDADE FEDERAL DO PARANÁ)

MINISTÉRIO DA EDUCAÇÃO
SETOR DE CIÊNCIAS DA SAÚDE
UNIVERSIDADE FEDERAL DO PARANÁ
PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
PROGRAMA DE PÓS-GRADUAÇÃO ODONTOLOGIA - 40001016065P8

TERMO DE APROVAÇÃO

Os membros da Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação ODONTOLOGIA da Universidade Federal do Paraná foram convocados para realizar a arguição da tese de Doutorado de **GISELLE EMILÂINE DA SILVA REIS** intitulada: **Efeito de diferentes variáveis na percepção do desconforto cirúrgico durante a remoção de terceiros molares de mulheres**, sob orientação da Profa. Dra. RAFAELA SCARIOT, que após terem inquirido a aluna e realizada a avaliação do trabalho, são de parecer pela sua APROVAÇÃO no rito de defesa.

A outorga do título de doutora está sujeita à homologação pelo colegiado, ao atendimento de todas as indicações e correções solicitadas pela banca e ao pleno atendimento das demandas regimentais do Programa de Pós-Graduação.

CURITIBA, 30 de Outubro de 2023.

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Dedico este trabalho ao meu maior tesouro, minha família, pelo amor e apoio a este e outros projetos de minha vida.

AGRADECIMENTOS

Desde que eu iniciei minha graduação em Odontologia na Universidade Federal do Paraná, eu encontrei tantas pessoas excepcionais, sim, EXCEPCIONAIS e digo isso sem medo de exageros...Em toda a minha trajetória, eu estive cercada de "pessoas que abrem portas" - são aquelas que chegam antes e não tem receio de ajudar mais pessoas a chegar onde elas chegaram – eu sei que encontrar essas pessoas é raridade e sou grata por cada porta que me foi aberta.

A Professora Rafaela, eu não poderia iniciar esse texto com outra pessoa. Muito obrigada por ter me acolhido no mestrado e ter me ensinado tantas coisas ao longo desses 6 anos. Foi uma honra ter tido a oportunidade de ter você como minha orientadora. Obrigada por sempre depositar tanta confiança em mim, por ter me ensinado sobre trabalhar em equipe, liderança e, principalmente, a como ser uma boa pesquisadora. Eu sempre me espelhei muito em você, pois para mim você transmite força e segurança. Te admiro muito.

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A professora Yasmine, sou muito feliz e grata por há quase 8 anos nossos caminhos terem se cruzado e desde o primeiro contato, nunca mais termos deixado de trabalhar juntas. Sempre tive muita admiração por você e você sempre foi exemplo para mim, de uma pessoa dedicada, batalhadora e que faz tudo de maneira impecável, colocando esmero e amor em cada detalhe a sua volta. Ao longo dessa trajetória, você se tornou uma grande amiga, pela qual tenho muito amor, carinho e respeito. Não tenho palavras para agradecer tudo o que você faz por mim, por todas as portas que já me abriu e por tudo o que já me ensinou.

A Professora Juliana Feltrin, obrigada por estar sempre disposta a ajudar na construção de meus trabalhos acadêmicos, você contribuiu muito com a minha formação, admiro a excelente profissional que você é e me espelho muito em você. Obrigada por ter aceitado fazer parte da minha banca avaliadora.

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A Idalina, obrigada por ter aceitado com tanta solicitude a ajudar no desenvolvimento deste trabalho. Ter compartilhado as tardes de terça e quinta feira com você nos últimos anos, tornou meus dias mais felizes.

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Aos residentes, obrigada por possibilitarem, através da realização dos procedimentos cirúrgicos, que esse trabalho fosse executado.

A todos os professores da Universidade Federal do Paraná que contribuíram com a minha formação profissional e pessoal. Agradeço especialmente, ao professor Nelson, meu orientador de mestrado, ao Professor Cassius, meu orientador durante a graduação e eterno tutor e ao Professor Daniel Bonotto.

Aos funcionários da Universidade Federal do Paraná.

As pacientes que participaram desse estudo.

A minha amiga de mestrado e da vida, Maria Fernanda. Eu nunca poderei agradecer o suficiente por tudo o que já fez por mim. Obrigada por estar sempre presente em minha vida.

Aos meus amigos, em especial a Brunna e Jullyana (minha eterna duplinha). Obrigada por se fazerem presentes em minha vida nas horas que eu mais precisei, eu amo vocês!

A minha família (Mãe, Pai, Matheus e Jean), obrigada pelo amor e apoio incondicionais que vocês sempre me proporcionaram, em todas as etapas da minha vida. Eu amo vocês, do fundo do meu coração.

RESUMO

Procedimentos para remoção de terceiros molares são rotineiros na prática odontológica e requerem conhecimento técnico e científico. Com o intuito de aprimorar o cuidado centrado no paciente, faz-se necessária a investigação das variáveis relacionadas ao desconforto cirúrgico. Esse estudo transversal observacional foi dividido em dois artigos, o primeiro artigo investigou o efeito das variáveis individuais, relacionadas a saúde da mulher, cirúrgicas, anatômicas e ansiedade sob a percepção do desconforto e o segundo verificou a influência de polimorfismos nos genes *COMT*, *SLC6A4*, *TRPV1*, *HTR2A*, *ESR1* e *ESR2* na percepção de desconforto durante a remoção de terceiros molares. Foram incluídas 200 mulheres, entre 18 e 45 anos, atendidas no serviço de Cirurgia e Traumatologia Bucomaxilofaciais da Universidade Federal do Paraná, durante o período de 24 meses. O desconforto cirúrgico foi avaliado através do questionário de autopercepção de cirurgia bucal (QCirDental). Variáveis individuais (idade, raça, índice de massa corporal [IMC]), variáveis relacionadas a saúde da mulher (fase do ciclo menstrual, níveis hormonais, uso de métodos contraceptivos, número de filhos, presença de dor crônica e orofacial), variáveis cirúrgicas (experiência do cirurgião, duração do procedimento cirúrgico, número de dentes removidos, necessidade de osteotomia e/ou odontosecção), variáveis anatômicas (curvatura radicular, divergência radicular, proporção coroa/raiz e classificação radiográfica de Winter), variáveis relacionadas a ansiedade (IDATE traço e estado, experiência e trauma em cirurgias odontológicas anteriores, medicamentos para ansiedade ou depressão) foram avaliadas. Amostras de sangue foram obtidas a fim de verificar o nível dos hormônios progesterona, estradiol e FSH. O DNA genômico do participante foi coletado através de raspagem da mucosa jugal. Os polimorfismos avaliados foram genotipados pela técnica de reação da cadeia em polimerase (PCR). Os dados foram submetidos a análise estatística através do software SPSS 25, com nível de significância de 5%. Como resultados, foi verificado que a mediana do desconforto cirúrgico de 1,50. IMC mais altos (*p=0,042*), fase folicular do ciclo menstrual (*p=0,033*), não ser mãe (*p=0,047*), menor número de filhos (*p=0,047*), maior duração do procedimento cirúrgico (*p=0,012*), traço de ansiedade alto (*p<=0,01*), experiência traumática em cirúrgica anterior (*p=0,021*), uso de medicação para ansiedade e depressão (*p=0,016*), foram associados a maior percepção de desconforto durante a remoção de terceiros molares. Além disso, genótipo TT para o polimorfismo *rs174675* em *COMT* no modelo aditivo e dominante (*p=0,014*) e (*p<=0,01*) respectivamente, genótipo GG para o polimorfismo *rs6113* em *HTR2A* no modelo dominante (*p=0,038*) foram variáveis associadas a maior percepção do desconforto durante a remoção de terceiros molares. Os resultados encontrados nesse estudo sugerem que diferentes fatores estão envolvidos na percepção do desconforto, tais como: IMC, ciclo menstrual, maternidade, número de filhos, duração do procedimento cirúrgico, traço de ansiedade, experiência traumática prévia, uso de medicamentos para ansiedade e depressão, polimorfismo rs174675 na COMT para mulheres com genótipo TT e o polimorfismo rs6313 em HTR2A para o genótipo GG. Isto reforça os princípios preconizados pelo modelo biopsicossocial. Enfatizando a necessidade de tratamento individualizado, priorizando o bem-estar dos pacientes submetidos à remoção de terceiros molares.

Palavras-chave: cirurgia bucal; terceiro molar; ciclo menstrual; polimorfismos genéticos; percepção do paciente.

ABSTRACT

The removal of third molars is routine in dental practice and requires technical and scientific knowledge. In order to improve patient-centered care, it is necessary to investigate variables related to surgical discomfort. This cross-sectional observational study was divided into two articles. The first article investigated the effect of individual variables related to women's health, surgical aspects, anatomy, and anxiety on the perception of discomfort. The second article examined the influence of polymorphisms in the genes COMT, SLC6A4, TRPV1, HTR2A, ESR1, and ESR2 on discomfort perception during the removal of third molars. A total of 200 women aged 18 to 45, treated at the Oral and Maxillofacial Surgery and Traumatology Service of the Federal University of Paraná over a 24-month period, were included in the study. Surgical discomfort was assessed using the Oral Surgery Self-Perception Questionnaire (QCirDental). Various variables were evaluated, including individual factors (age, race, body mass index [BMI]), women's health-related variables (menstrual cycle phase, hormonal levels, contraceptive use, number of children, presence of chronic orofacial pain), surgical variables (surgeon experience, surgical procedure duration, number of teeth removed, need for osteotomy and/or odontosection), anatomical variables (root curvature, root divergence, crown/root ratio, and Winter's radiographic classification), and anxiety-related variables (state and trait anxiety, previous dental surgery experience, anxiety or depression medication). Blood samples were obtained to measure progesterone, estradiol, and FSH hormone levels. Genomic DNA was collected through buccal mucosa scraping, and polymorphisms were genotyped using the polymerase chain reaction (PCR) technique. The data were analyzed statistically using SPSS 25 software with a significance level of 5%. The results showed that the median surgical discomfort was 1.50. Higher BMI ($p=0.042$), follicular phase of the menstrual cycle ($p=0.033$), not being a mother ($p=0.047$), fewer children ($p=0.047$), longer surgical procedure duration ($p=0.012$), high anxiety trait ($p<=0.01$), traumatic experience in previous surgery ($p=0.021$), and use of anxiety and depression medication ($p=0.016$) were associated with a higher perception of discomfort during the removal of third molars. Additionally, the TT genotype for the rs174675 polymorphism in COMT in both additive and dominant models ($p=0.014$) and ($p<=0.01$) respectively, and the GG genotype for the rs6113 polymorphism in HTR2A in the dominant model ($p=0.038$) were variables associated with a higher perception of discomfort during the removal of third molars. The findings suggest that various factors contribute to discomfort perception, including BMI, menstrual cycle, motherhood, number of children, surgical procedure duration, anxiety trait, previous traumatic experience, and specific gene polymorphisms. This reinforces the principles of the biopsychosocial model and emphasizes the need for individualized treatment, prioritizing the well-being of patients undergoing the removal of third molars.

Keywords: oral surgery; molar third; menstrual cycle; polymorphism genetic; patient perception.

LISTA DE FIGURAS

LISTA DE SIGLAS

BiOS-Q - *Burdens in Oral Surgery Questionnaire*

BiPD-Q - *Burdens in Prosthetic Dentistry Questionnaire*

COMT - *Catecol-O-metiltransferase*

CTBMF - Cirurgia e Traumatologia Buco-Maxilo-Faciais

DNA - Ácido desoxirribonucleico

ESR1 - *Gene α do Receptor de Estrogênio Humano*

ESR2 - *Gene β do Receptor de Estrogênio Humano*

FSH - Hormônio folículo estimulante

HTR2A - *Receptor de 5-hidroxitriptamina 2A*

IMC - Índice de massa corporal

LH - Hormônio luteinizante

LSD - Dietilamida do ácido lisérgico

PCR - Reação em cadeia da polimerase

QCirDental - Questionário de autopercepção de cirurgia bucal

RPM - Rotações por minuto

SLC6A4 - *Portador de Soluto Família 6 membro 4*

SPSS - *Statistical Packger for Social Science*

SSRI - Inibidor seletivo da receptação de serotonina

STREGA - *STrengthening the REporting of Genetic Association Studies*

TRPV1 - *Canal Cationico da Subfamília V do Potencial de Receptor Transitório, Membro 1*

UFPR - Universidade Federal do Paraná

SUMÁRIO

1 INTRODUÇÃO E REVISÃO DE LITERATURA

1.1 FATORES QUE PODEM INFLUENCIAR A PERCEPÇÃO DE DESCONFORTO DURANTE A REMOÇÃO DE TERCEIROS MOLARES

A remoção de terceiros molares é realizada rotineiramente. Até o momento poucos estudos se dedicaram a avaliar a percepção do paciente sobre o procedimento no momento trans cirúrgico ou pós-operatório imediato (REIS et al., 2020; CALIXTO et al., 2022), sendo essa uma característica de importante observação, pois, dessa forma pode-se aprimorar o cuidado centrado no paciente.

Nas últimas décadas a perspectiva do paciente como um critério de qualidade do tratamento, tornou-se cada vez mais relevante (BULLINGER, 2002). Contudo, na odontologia existem apenas três instrumentos desenvolvidos para avaliar a percepção do paciente sobre o tratamento recebido, o *Burdens in Oral Surgery Questionnaire* (BiOS-Q), o *Burdens in Prosthetic Dentistry Questionnaire* (BiPD-Q) e o Questionário de autopercepção de cirurgia bucal (QCirDental) (REISSMANN et al., 2013; REISSMANN et al., 2013; BORTOLUZZI et al., 2018).

Para a cirurgia bucal, existem apenas dois instrumentos disponíveis para avaliar a percepção do paciente no momento transoperatório, o BiOS-Q e o QCirDental. O BiOS-Q é composto por 16 questões incluindo sete perguntas relacionadas a anestesia, cinco sobre pressões e vibração e uma questão para barulhos, gosto, dor e tempo cirúrgico (REISSMANN et al., 2013). O QCirDental é composto por 20 questões sobre as sensações desagradáveis e os desconfortos relacionados a remoção dentária. O instrumento considera estado de tensão, dor, angústia, percepções sobre a privacidade, o ambiente em que a remoção cirúrgica dentária foi realizada e questões relacionadas a perda dentária (BORTOLUZZI et al., 2018).

A importância do uso de um instrumento de medida que avalie as percepções, incômodos e sensações do paciente se traduz na alternativa de avaliação da qualidade de cuidados e serviços oferecidos, gerando condições de reconhecer indivíduos vulneráveis com o intuito de melhor orientar ações preventivas e protetoras aos pacientes (BORTOLUZZI et al., 2018).

1.1.1 FATORES INDIVIDUAIS E BIOPSICOSSOCIAIS

A dor é uma experiência subjetiva e altamente pessoal, definida pela associação internacional para estudos da dor, como: "uma experiência sensitiva e emocional desagradável associada, ou semelhante àquela associada, a uma lesão tecidual real ou potencial" (RAJA et al., 2020). Ocorrem importantes diferenças individuais na percepção dolorosa, as quais produzem experiências que são completamente únicas à pessoa que as experimenta (FILLINGIM, 2017). Um desafio bem reconhecido resultante da natureza subjetiva da dor é a impossibilidade de medi-la diretamente, ao contrário, devemos contar com o autorrelato dos indivíduos para obter um indício da sua experiência (FILLINGIM, 2017).

É proposto na literatura um modelo biopsicossocial que contemple as diferenças individuais para o estudo da dor (GATCHEL, 2004; FILLINGIM, 2017). Este modelo postula que a experiência da dor é influenciada por complexas e dinâmicas interações entre múltiplos fatores biológicos, psicológicos e sociais. Acredita-se que sexo, etnia, histórico médico, genética e características psicossociais influenciem na experiência dolorosa (GATCHEL, 2004; FILLINGIM, 2017).

Em relação ao gênero, a literatura aponta que a dor crônica é mais prevalente em mulheres do que em homens (BIMPONG et al., 2021). Além disso, diferentes estudos que examinaram a dor pós-cirúrgica em procedimentos médicos, como colecistectomia (DE COSMO et al., 2008), colonoscopia (LEE et al., 2006), destacam a diferença da percepção de dor transoperatória ou pós-operatória imediata em relação ao gênero, com as mulheres apresentando maior percepção dolorosa. Em relação a cirurgia para remoção de terceiros molares, um estudo verificou se havia diferença na percepção de dor, trismo e edema em relação ao gênero e não encontrou associações significativas (SILVA et al., 2021).

Um tópico de interesse é se indivíduos de diferentes origens raciais experimentam a dor de forma diferente (FILLINGIM, 2017). Uma meta análise que examinou a percepção da dor em adultos saudáveis encontrou que os afro-americanos exibem maior sensibilidade experimental à dor, quando comparados aos indivíduos brancos (RAHIM-WILLIAMS et al., 2012).

1.1.2 CARACTERÍSTICAS RELACIONADAS A SAÚDE DA MULHER

Há tempos a literatura aponta que ocorre uma disparidade de gênero na dor, com as mulheres apresentando maior sensibilidade e menor tolerância à dor, além de maior somatização dolorosa, quando comparadas aos homens (FILLINGIM & MAIXNER, 1995; RILEY et al., 1998; WIESENFELD-HALLIN, 2005; FILLINGIM et al., 2009). A diferença sexual mais bem estabelecida em relação a dor, diz respeito as condições de dor crônica, em que as mulheres são de 2 a 6 vezes mais acometidas, quando comparadas aos homens (UNRUH, 1996; AMANDUSSON & BLOMQVIST, 2013). Sendo assim, a disparidade de gênero na dor é preocupante e políticas publicas devem ser desenvolvidas para elaborar futuras estratégias de prevenção e gestão (BIMPONG et al., 2021). Não se sabe exatamente as razões das mulheres serem mais suscetíveis a dor. No entanto, existem evidências de que a intensidade dos sintomas de dor crônica flutua de acordo com as fases do ciclo menstrual (JOHANNES et al., 1995; HOUGHTON et al., 2002; LERESCHE et al., 2003).

1.1.2.1 CICLO MENSTRUAL

O conhecimento sobre o ciclo menstrual e seu mecanismo fisiológico é de grande importância para a compreensão das diversas modificações biológicas que ocorrem a cada fase do ciclo e repercutem de maneira global sobre o organismo feminino (LOUREIRO et al., 2011). O ciclo menstrual normal varia de 21 a 35 dias, com média de 28 dias. Por convenção, o primeiro dia de sangramento vaginal é considerado o primeiro dia do ciclo menstrual, que pode ser dividido em três fases distintas: folicular, ovulatória e lútea (SCHMALENBERGER et al., 2021).

A fase folicular é caracterizada por baixos níveis de estrogênio e progesterona, que fazem com que o revestimento uterino degenere e se desprenda na menstruação, marcando o primeiro dia do ciclo (SCHMALENBERGER et al., 2021). Um aumento nos níveis de hormônio luteinizante (LH) e folículo-estimulante (FSH) assinalam o início da fase ovulatória, na qual o nível de estrogênio atinge seu máximo e a progesterona se eleva. Na fase lútea os hormônios LH e FSH diminuem, o folículo se fecha após soltar-se do óvulo e forma o corpo lúteo, que segrega progesterona (SCHMALENBERGER et al., 2021). Caso o óvulo não seja fertilizado, o corpo lúteo

se degenera e deixa de produzir progesterona, o nível de estrogênio diminui e se inicia um novo ciclo menstrual (SCHMALENBERGER et al., 2021).

1.1.2.2 NÍVEIS HORMONAIS

Em cada fase do ciclo menstrual, ocorre uma variação nos padrões hormonais. A possibilidade da relação entre os níveis de hormônios sexuais e o limiar da dor nas mulheres começava a ser discutido há 90 anos (HERREN, 1933). Daquele tempo até o presente, muitos estudos foram conduzidos com o objetivo de conhecer melhor como se dá essa relação (FILLINGIM et al., 1997; LERESCHE et al, 1997; TSEN et al., 2001; LERESCHE et al., 2003; WIJNHOVEN et al., 2006; STENING et al., 2007; STENING et al., 2012; LEE et al., 2014; KASHANIAN et al., 2019; POGATZKI-ZAHN et al., 2019).

A literatura aponta que os aumentos nos níveis de progesterona são associados a analgesia, isso é especialmente observado durante a gestação, em que esse aumento ocorre de forma considerável (GINTZLER & BOHAN, 1990). Com relação as oscilações durante o ciclo menstrual, as evidências não são conclusivas, enquanto alguns estudos mostram que quando seus níveis séricos estão mais altos, as mulheres tendem a possuir uma menor percepção dolorosa (LEE et al., 2014; KASHANIAN et al., 2019). Há evidência apontando que na dor pós-cirúrgica, a fase luteal, ou seja, quando os níveis de progesterona estão mais altos, as mulheres relatam maior sensibilidade dolorosa e hiperalgesia (POGATZKI-ZAHN et al., 2019).

Diferentes estudos com mulheres saudáveis mostram maior sensibilidade à dor durante períodos de baixos níveis de estrogênio (LERESCHE et al., 2003; STENING et al., 2007) enquanto outros estudos relatam resultados controversos (FILLINGIM et al., 1997; LERESCHE et al, 1997; TSEN et al., 2001; WIJNHOVEN et al., 2006; STENING et al., 2012).

Não há estudos associando oscilações nos parâmetros de FSH e percepção de dor. No entanto, o FSH desempenha papel fundamental durante o ciclo menstrual. FSH estimula o crescimento dos folículos ovarianos, e LH desencadeia a liberação do oócito pelo folículo dominante, demarcando a ocorrência da ovulação. Tanto os níveis de FSH quanto de LH apresentam variações sistemáticas ao longo do ciclo natural, incluindo um pico pré-ovulatório (SCHMALEMBERGER et al., 2021).

Ao nosso conhecimento, esse é o primeiro estudo com o objetivo de verificar se hormônios relacionados ao ciclo menstrual influenciam na percepção de desconforto durante a remoção de terceiros molares.

1.1.3 CARACTERÍSTICAS CIRÚRGICAS, ANATÔMICAS E RADIOGRÁFICAS

Diferentes variáveis individuais e cirúrgicas influenciam na dificuldade da remoção dentária (RENTON et al., 2001; YUASA et al., 2002; BENEDIKTSDÓTTIR et al., 2004; SUSARLA & DODSON, 2004; SUSARLA & DODSON, 2005; GBOTOLORUN et al., 2007). Existem evidências de que a experiência do cirurgião dentista (BENEDIKTSDOTTIR et al., 2004), o tempo de duração do procedimento cirúrgico (BENEDIKTSDOTTIR et al., 2004) e a realização de retalho cirúrgico (BORTOLUZZI et al., 2018) podem estar associados com a dificuldade para a remoção de terceiros molares. No entanto, em estudo conduzido por REIS e colaboradores, em 2020, não foram encontradas variáveis cirúrgicas associadas a percepção de desconforto na remoção de terceiros molares, sugerindo que o nível de dificuldade do procedimento cirúrgico pode não impactar na percepção do desconforto.

A associação das características anatômicas com a percepção do desconforto durante a remoção de terceiros molares deve ser considerada. HUPP e colaboradores, em 2015, descreveram os principais fatores anatômicos que influenciam no nível de dificuldade da cirurgia para remoção dentária, sendo: nível de abertura bucal, grau de mobilidade do dente e condição da coroa, número de raízes, curvatura radicular, grau de divergência radicular, tamanho das raízes e presença de reabsorção interna ou externa radicular. Em relação aos terceiros molares, a profundidade de impactação, angulação e morfologia da raiz, tecido de impactação (tecido mole ou tecido ósseo) e número de dentes extraídos num mesmo procedimento cirúrgico são características que devem ser consideradas (AKADIRI & OBIECHINA, 2009).

A classificação de Winter é frequentemente adotada para auxiliar na avaliação pré cirúrgica do terceiro molar a ser removido (WINTER, 1923). Ela determina a angulação do longo eixo de terceiros molares com relação ao longo eixo de segundos molares adjacentes, classificando os dentes, por ordem de dificuldade em: mesioangular, vertical, horizontal e distoangular (Figura 1). Outra classificação

tradicionalmente utilizada antes da remoção de terceiros molares é a classificação de Pell & Gregory (PELL & GREGORY, 1933). Contudo, existe evidência da ineficácia do uso desta classificação na associação entre predição de dificuldade cirúrgica para remoção de terceiros molares e percepção de desconforto (GARCIA et al., 2000; REIS et al., 2020).

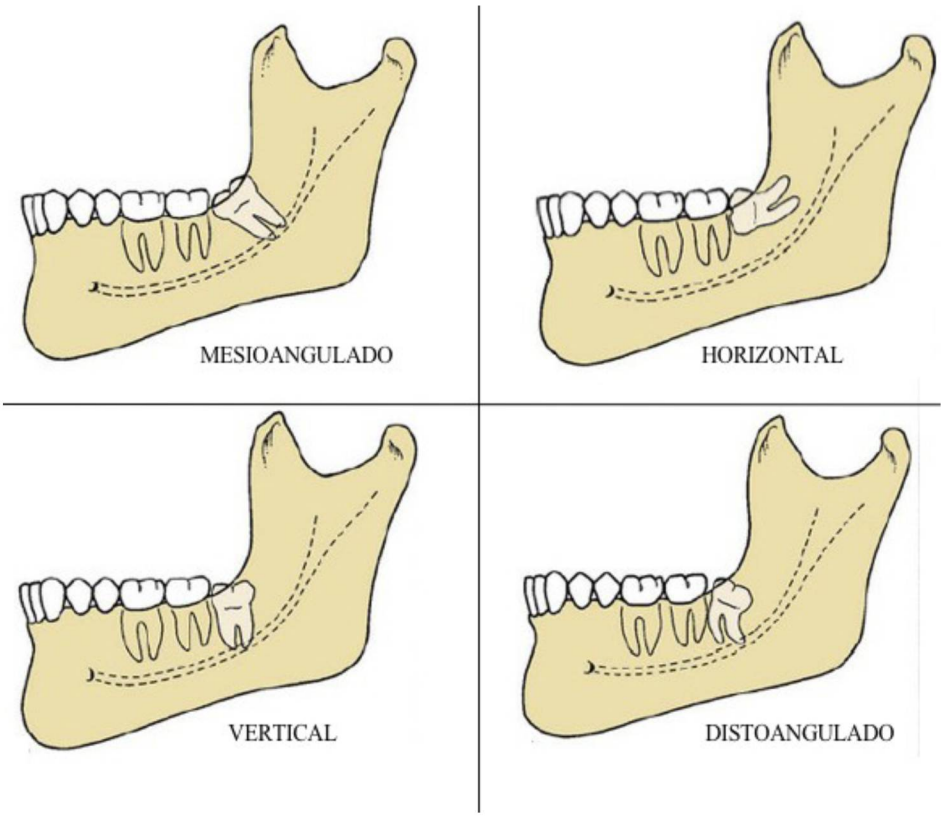


Figura 1 – Classificação da posição dos terceiros molares segundo Winter (Adaptada de Hupp et al., 2015) Fonte: Hupp JRE, Edward T, Myron R. Cirurgia Oral e Maxilofacial Contemporânea. Elsevier, editor. Rio de Janeiro. 2015.

1.1.4 VARIÁVEIS RELACIONADAS A ANSIEDADE

Fatores psicossociais em interação com outras características influenciam na percepção dolorosa. Estudos que induziram dor aguda experimental em pacientes depressivos encontraram um limiar de dor mais baixo, quando comparados a indivíduos não depressivos (ZAMBITO et al., 2015; HERMESDORF et al., 2016; NITZAN et al., 2019).

Em relação a ansiedade, há indícios de correlação com a dor aguda, sendo que quanto maior a pontuação da ansiedade antes da cirurgia, piores eram as dores pós-operatórias percebidas (CARR et al., 2005). Além disso, foi identificado que a

ansiedade pré-operatória é preditiva da ansiedade pós-operatória (CARR et al., 2005). Um estudo que avaliou a associação entre ansiedade e percepção de dor durante cirurgia de implante dentário demonstrou que a ansiedade dentária pode aumentar a percepção de dor dos pacientes durante a cirurgia de implante oral (ZHANG et al., 2019).

1.1.5. POLIMORFISMOS GENÉTICOS

Os genes são unidades estruturais de DNA (ácido desoxirribonucleico), compostos por sequências de nucleotídeos. Variações nessas sequências que ocorrem na população de forma estável, e que são encontradas com frequência de 1% ou mais, são denominados polimorfismos genéticos. Os polimorfismos são responsáveis pela variabilidade dos indivíduos (BALASUBRAMANIAN et al., 2004). As interações gene-demográficas têm profundas implicações metodológicas e clínicas (FILLINGIM, 2017).

A investigação científica ainda se esforça para revelar as bases genéticas dos fenótipos associados a percepção dolorosa. O valor final na compreensão dos determinantes genéticos da dor é ser capaz de reduzir o sofrimento nas populações humanas (YOUNG et al., 2012). O objetivo da compreensão genética associada a características individuais busca por terapias medicamentosas de alta precisão, adaptadas à predisposição individual (SLADE et al., 2021), que maximizem os resultados terapêuticos e minimizem os efeitos secundários (DIATCHENKO et al., 2007).

A literatura atual investiga, por exemplo, dosagens analgésicas ideais baseadas em polimorfismos genéticos para serem utilizadas no contexto clínico (CHENG et al., 2022), além de buscar meios para facilitar a realização de genotipagem dos pacientes (DE OLAZARRA et al., 2022). Os tratamentos personalizados serão provavelmente o futuro da medicina nas mais diversas áreas, no entanto, a individualização é de particular importância no manejo de condições associadas a sensibilidade, percepção e dor devido à elevada variabilidade individual encontrada nessas características (DIATCHENKO et al., 2005; NIELSEN et al., 2009; YOUNG et al., 2012; PERRY et al., 2019). Sendo assim, o conhecimento da predisposição genética oferece um grande potencial para o futuro na individualização dos

tratamentos, promovendo uma compreensão profunda da condição de cada individuo (VETTERLEIN et al., 2023).

É importante enfatizar que outros fatores, tais como: ambiente sociocultural, cognitivo, experiências anteriores e fatores fisiológicos irão influenciar na percepção de dor e desconforto dos indivíduos, como bem pontuado no modelo biopsicossocial (GATCHEL, 2004; FILLINGIM, 2017). No entanto, a literatura demonstrou que uma grande proporção de relações pode ser explicada através da predisposição genética (YOUNG et al., 2012). Estudos realizados com gêmeos estimaram uma herdabilidade de 22 a 60% para sensibilidade à dor (NORBURY et al., 2007; Nielsen et al., 2008) e uma herdabilidade de 21 a 67% para condições de dor crônica (NIELSEN et al., 2012; FERREIRA et al., 2013; VISSCHER & LOBBEZOO, 2015).

Entre os genes mais estudados para condições de percepção e dor tem-se: *catecol-O-metiltransferase* (*COMT*), *Portador de Soluto Família 6 membro 4* (*SLC6A4*), *Canal Cationico da Subfamília V do Potencial de Receptor Transitório, Membro 1 (TRPV1), Receptor de 5-hidroxitriptamina 2A (HTR2A) e gene α e β do receptor de estrogênio humano* (*ESR1* e *ESR2*) (VETTERLEIN et al., 2023).

Catecol-O-metiltransferase (COMT)

A *COMT* é um gene codificador de proteínas localizado no braço longo do cromossomo 22, na posição 22q11.21 (Figura 2). Catalisa a transferência de um grupo metil da S-adenosilmetionina para as catecolaminas, incluindo os neurotransmissores dopamina, epinefrina e norepinefrina. Esta O-metilação resulta em uma das principais vias de degradação dos transmissores de catecolaminas. Além de seu papel no metabolismo de substâncias endógenas, a *COMT* é importante no metabolismo de drogas catecol utilizadas no tratamento da hipertensão, asma e doença de Parkinson (YAGER & LIEHR, 1996; YAGER & DAVIDSON, 2006).

As doenças associadas à *COMT* incluem esquizofrenia (SAGUD et al., 2023), depressão resistente ao tratamento (WANG et al., 2022), ansiedade (CHMIELOWIEC et al., 2022), condições dolorosas (VETTERLEIN et al., 2023) e transtornos psicóticos (VIEIRA et al., 2023).

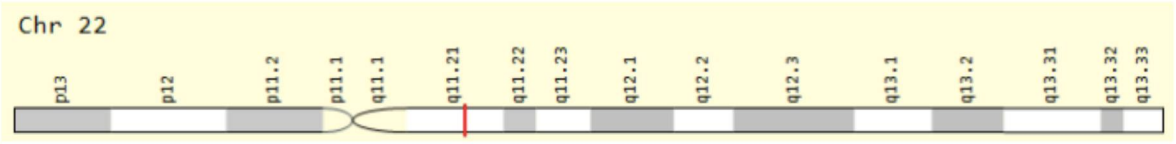


Figura 2. Localização genômica do gene *COMT*. Disponível em: https://www.genecards.org/cgi-bin/carddisp.pl?gene=COMT&keywords=COMT.

Portador de Soluto Família 6 membro 4 (SLC6A4)

O *SLC6A4* é um gene que codifica a proteína 5-HTT, transportadora de serotonina dependente de sódio e cloreto (HASENHUETL et al., 2016; YANG & GOUAUX, 2021), localizado no cromossomo 17, na posição 17q11,1-p12 (Figura 3). Possui função essencial para a homeostase da serotonina no sistema nervoso central. No córtex somatossensorial em desenvolvimento, atua nos neurônios glutamatérgicos para controlar a captação de serotonina e suas funções tróficas. No córtex maduro, atua nos neurônios da rafe do tronco cerebral para mediar a captação de serotonina da fenda sináptica de volta ao terminal pré-sináptico, encerrando assim a sinalização da serotonina na sinapse. Regula os níveis de serotonina no sangue (BRENNER et al., 2007).

A proteína transportada por esse gene é alvo de estimulantes psicomotores, tais como anfetaminas e cocaína e, além de ser alvo de muitos medicamentos antidepressivos do SSRI (Inibidor seletivo da receptação de serotonina) e da classe dos antidepressivos tricíclicos.

Esquizofrenia (GHAMARI et al., 2022), traços psicopáticos (HOLLERBACH et al., 2021) e comportamentos suicidas (RAFIKOVA et al., 2021) são associados ao *SLC6A4*.

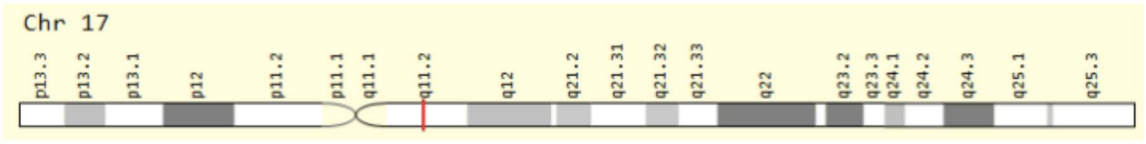


Figura 3. Localização genômica do gene *SLC6A4*. Disponível em: https://www.genecards.org/cgi-bin/carddisp.pl?gene=SLC6A4&keywords=SLC6A4.

Canal Cationico da Subfamília V do Potencial de Receptor Transitório, Membro 1 (*TRPV1*)

O gene *TRPV1* está localizado no cromossomo 17, na posição 17p13.13 (Figura 4). Possui função importante na detecção de estímulos químicos e térmicos

nocivos, através de canal catiônico permeante de cálcio não seletivo. Envolvido na mediação da dor inflamatória e hiperalgesia. Atua como receptor endocanabinóide ionotrópico com efeitos neuromoduladores centrais. Desencadeia uma forma de depressão de longo prazo mediada pelo endocanabinoide anandamina no hipocampo e no núcleo accumbens, afetando a endocitose dos receptores AMPA (HAYES et al., 2000; MCINTYRE et al., 2001; CORTRIGHT et al., 2001).

O *TRPV1* foi associado à sensibilidade dolorosa (SHUFANG et al., 2023), tendo importante papel na dor associada ao câncer (DUITAMA et al., 2021), além da expressão de *TRPV1* ter sido correlacionada ao nível de dor em mulheres com endometriose (SONG et al., 2012).

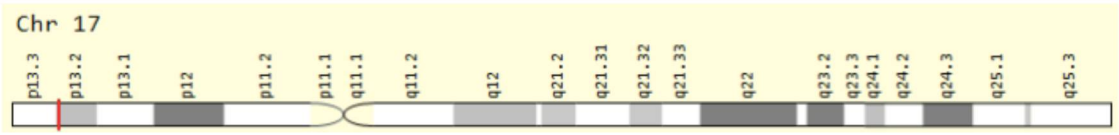


Figura 4. Localização genômica do gene *TRPV1*. Disponível em: https://www.genecards.org/cgi-bin/carddisp.pl?gene=TRPV1&keywords=TRPV1.

Receptor de 5-hidroxitriptamina 2A (*HTR2A*)

O gene *HTR2A* está localizado no cromossomo 13, na posição 13q14.2 (Figura 5). É responsável por codificar um dos receptores da serotonina, um neurotransmissor que desempenha papel crucial na comunicação entre células nervosas. O gene *HTR2A* possui instruções para a síntese do receptor 5-HT2A, uma proteína que está incorporada à membrana celular e faz parte da família de receptores acoplados à proteína G (STAM et al., 1992). Devido a ação relacionada a serotonina, afeta a atividade neural, percepção, cognição e humor (GONZÁLEZ-MAESO et al., 2008).

Funciona como receptor para várias drogas e substâncias psicoativas, incluindo mescalina, psilocibina, 1-(2,5-dimetoxi-4-iodofenil)-2-aminopropano e dietilamida do ácido lisérgico (LSD) (WACKER et al., 2017).

Polimorfismos no gene *HTR2A*, foram associadas a diferenças individuais na resposta a medicamentos psiquiátricos e a susceptibilidade a certos transtornos mentais, como transtorno obsessivo compulsivo (DICKEL et al., 2007), transtornos depressivos e esquizofrenia (D'HAENE et al., 1992; LÓPEZ-FIGUEROA et al., 2004).

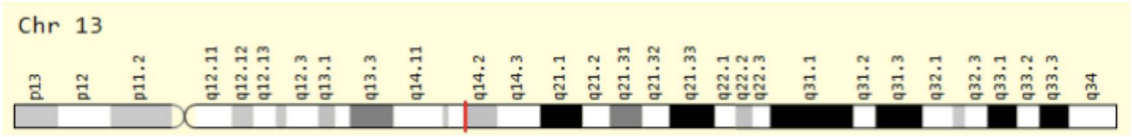


Figura 5. Localização genômica do gene *HTR2A*. Disponível em: https://www.genecards.org/cgi-bin/carddisp.pl?gene=HTR2A&keywords=HTR2A.

RECEPTORES DE ESTERÓIDES SEXUAIS

Os receptores de esteroides sexuais são fatores de transcrição ativados por ligantes que se conectam a elementos específicos de resposta hormonal em seus genes alvo. Eles são abundantes em áreas cerebrais que possuem papel crucial na regulação das emoções, cognição e comportamento, tais como: hipotálamo, amígdala, córtex cerebral, hipocampo e tronco cerebral (PFAFF, 1968; MCEWEN, 2001; OSTERLUND & HURD, 2001).

Há dois subtipos de receptores de estrogênio: α e β (KUIPER et al., 1996). Além disso, diversas isoformas de cada subtipo foram relatadas (HIRATA et al., 2003). Os dois subtipos de receptores de estrogênio têm afinidades comparáveis pelo estradiol, mas muitos outros ligantes mostram ligação preferencial a um ou outro deles. Os dois subtipos também diferem em relação à distribuição nos tecidos e interações com co-reguladores (NILSSON et al., 2001; LONARD & O'MALLEY, 2006).

Gene α do Receptor de Estrogênio Humano (*ESR1*)

O *ESR1* está localizado no cromossomo 6, na posição 6q25.160 e é composto por 8 exons (Figura 6). Foram identificados muitos polimorfismos neste gene (SCHUBERT et al., 1999; HERRINGTON et al., 2002; HERRINGTON & HOWARD, 2003; GOLD et al., 2004). Devido ao papel do receptor de estrogênio α no desenvolvimento e função cerebral, diferentes estudos têm investigado associações entre o gene *ESR1* e diversos fenótipos comportamentais (WESTBERG & ERIKSSON, 2008).

Há evidências de associação entre *ESR1* e maior nível de ansiedade em homens (COMINGS et al., 1999), neuroticismo, psicoticismo e irritabilidade (WESTBERG et al., 2003). Além disso, em uma grande amostra da população idosa, foi encontrada associação entre o *rs2234693* e probabilidade de manifestação de

ansiedade em mulheres (TIEMEIER et al., 2005). Existe ainda, associações entre esse polimorfismo e depressão em mulheres chinesas (TSAI et al., 2003).

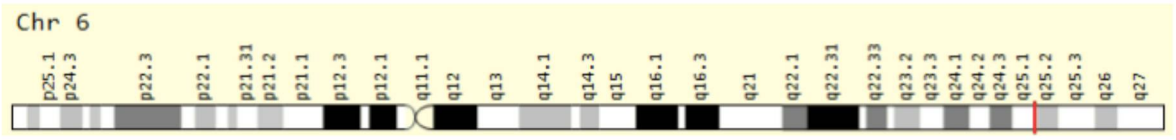


Figura 6. Localização genômica do gene *ESR1*. Disponível em: https://www.genecards.org/cgi-bin/carddisp.pl?gene=ESR1&keywords=ESR1.

Gene β do Receptor de Estrogênio Humano (*ESR2*)

O *ESR2* está localizado no cromossomo 14, na posição 14q22–24 (Figura 7). O gene é composto por 8 exons e possui várias polimorfias (ENMARK et al., 1997), das quais dois SNP são mais estudados, o *rs4986938* e o *rs1256049* (WESTBERG & ERIKSSON, 2008).

Diferentes investigações sugerem uma influência de variantes de *ESR2* no cérebro. Foram relatadas associações entre polimorfismos de *ESR2* e doença de Alzheimer (FORSELL et al., 2001; PIRSKANEN et al., 2005) e com doença de Parkinson de início precoce (WESTBERG et al., 2004). Evidências preliminares de um pequeno grupo de mulheres japonesas pós-menopáusicas sugerem uma associação entre queixas da menopausa, incluindo sintomas de humor e *ESR2* (TAKEO et al., 2005). Além disso, foi relatada associação entre *ESR2* e depressão em uma população adolescente (GENG et al., 2007). Dados em animais indicam que esse gene é de considerável importância para o comportamento, merecendo estudos adicionais (WESTBERG & ERIKSSON, 2008).

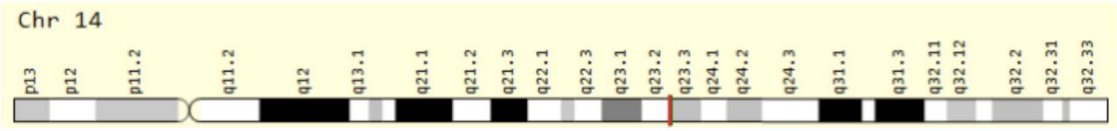


Figura 7. Localização genômica do gene *ESR2*. Disponível em: https://www.genecards.org/cgi-bin/carddisp.pl?gene=HTR2A&keywords=ESR2.

2. OBJETIVOS

2.1 OBJETIVO GERAL

Investigar fatores que influenciam na intensidade da percepção de desconforto cirúrgico durante a remoção de terceiros molares em mulheres.

2.2 OBJETIVOS ESPECÍFICOS

Avaliar a associação entre variáveis individuais, variáveis relacionadas a saúde feminina, ciclo menstrual, níveis hormonais, variáveis cirúrgicas, anatômicas e radiográficas e a percepção de desconforto durante a cirurgia para remoção de terceiros molares.

Avaliar associação entre ansiedade e percepção de desconforto durante a cirurgia para remoção de terceiros molares.

Investigar se polimorfismos associados aos genes *COMT*, SLC6A4, *TRPV1*, *HTR2A*, *ESR1* e *ESR2* são associados a percepção de desconforto durante a remoção de terceiros molares.

3. MATERIAIS E MÉTODOS

3.1 DESENHO DO ESTUDO E AMOSTRA

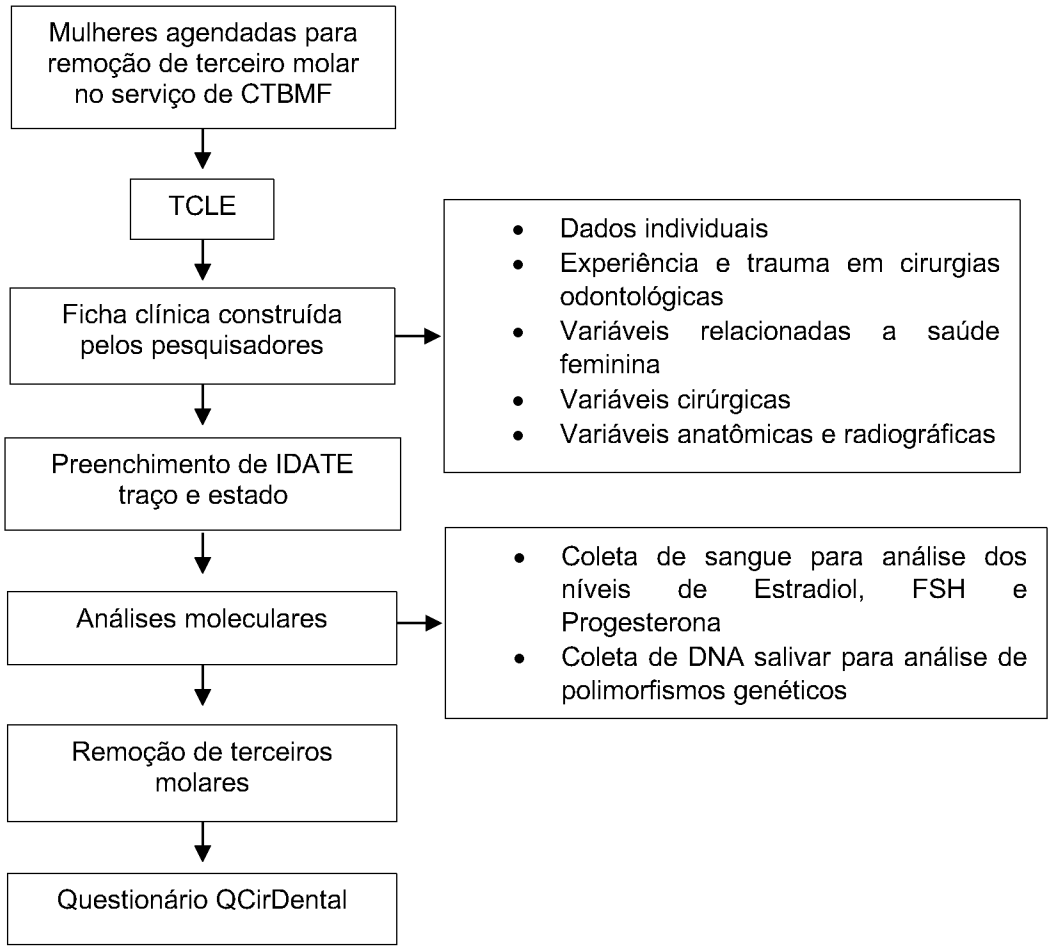
Este estudo contou com apreciação e aprovação do Comitê de Ética em Pesquisa da Universidade Federal do Paraná (UFPR) sob parecer CAAE 43894621.3.0000.0102 (ANEXO 1) e seguiu os princípios da declaração de Helsinki e as normas STREGA (LITTLE et al., 2009), caracterizando-se por ser um estudo transversal observacional com análise genética. O estudo foi realizado no período de agosto de 2021 a agosto de 2023 e incluiu 200 pacientes do serviço de Cirurgia e Traumatologia Buco-Maxilo-Faciais (CTBMF) do Curso de Odontologia da UFPR, agendadas para remoção de terceiros e que aceitaram participar da pesquisa. É importante ressaltar que no Serviço de Cirurgia os pacientes que apresentam infecção e/ou inflamação não são submetidos ao procedimento. Além disso, não existe um protocolo medicamentoso para controlar a ansiedade ou diminuir os sinais de inflamação no pré-operatório. Portanto, as participantes não faziam uso de nenhum medicamento antes da cirurgia.

Todas as participantes receberam as informações referentes a pesquisa, por meio do Termo de Consentimento Livre e Esclarecido (APÊNDICE 1) e, portanto, tiveram acesso aos objetivos e justificativas para a realização do estudo, bem como os benefícios e os riscos aos quais seriam expostas. Os critérios de inclusão foram: ser do sexo feminino, ter entre 18 e 45 anos de idade, passar por remoção de terceiros molares inclusos ou não inclusos no serviço de CTBMF da UFPR e aceitar participar do estudo. Os critérios de exclusão foram: gestantes, mulheres em período de amamentação, mulheres que realizassem terapias para reposição hormonal e menopausa.

A estimativa do tamanho da amostra para avaliar o desfecho do desconforto cirúrgico na remoção de terceiros molares foi realizada considerando os seguintes parâmetros: um tamanho populacional estimado de 400 mulheres/2 anos, uma frequência prevista de 50%, um limite de confiança de 5% e um efeito de desenho de 1. Utilizando estes parâmetros, os cálculos resultaram em um tamanho de amostra de 197 mulheres (www.openepi.com/samplesize). O número de 400 mulheres/2 anos é uma estimativa do número de mulheres que removem terceiros molares em dois anos no Centro cirúrgico de CTBMF.

3.2 ETAPAS DO ESTUDO

As pacientes agendadas para remoção de terceiros molares no serviço de CTBMF da UFPR foram convidadas a participar do estudo. Aquelas que aceitaram, foram avaliadas em sala separada. Os dados pessoais foram coletados e em seguida a participante respondeu ao instrumento IDATE. Posteriormente, foi realizada a coleta de sangue e de saliva. Os tubos cônicos tipo Falcon de centrífuga de 15 mL de cada paciente contendo a amostra genética foram armazenados a -20°C. O sangue foi centrifugado após 20 minutos da coleta e imediatamente encaminhado ao laboratório IDC Champagnat, local em que as análises foram realizadas. A paciente foi encaminhada à sala de cirurgia para remoção dentária, momento em que o examinador coletou os dados anatômicos, radiográficos e cirúrgicos. Ao final da cirurgia, após as orientações pós-operatórias, a paciente respondeu ao questionário QCirDental em sala separada (Fluxograma 1).



Fluxograma 1. Ilustração das etapas do estudo.

3.3 INSTRUMENTOS UTILIZADOS

3.3.1 FICHA CLÍNICA

A equipe de pesquisadores construiu uma ficha clínica objetiva (APÊNDICE 2) com o intuito de coletar os seguintes dados:

Dados individuais:

- Idade, índice de massa corporal (IMC) e raça.

Dados relacionados a saúde feminina:

- Fase do ciclo menstrual (paciente relatava a data do último ciclo menstrual, informando o primeiro e o último dia de menstruação).
- Uso de métodos contraceptivos: contraceptivo oral, contraceptivo injetável, adesivo transdérmico, dispositivo intrauterino (DIU) de levonogerstrel.
- Número de gestações, número de filhos.
- Presença de dor crônica ou dor orofacial.

Dados Cirúrgicos, anatômicos e radiográficos:

- Duração do procedimento cirúrgico (em minutos desde a chegada no centro cirúrgico até o término do procedimento).
- Número de terceiros molares removidos (≤ 2 dentes e > 2 dentes).
- Realização de osteotomia/odontosecção.
- Nível de curvatura radicular (pequeno ou grande).
- Nível de divergência radicular (pequeno ou grande).
- Proporção do tamanho da coroa em relação ao tamanho da raiz (coroa maior do que a raiz, coroa do tamanho da raiz, coroa menor do que a raiz).
- Classificação radiográfica de Winter.

Dados relacionados a ansiedade:

- Uso de medicação para tratamento de quadros psiquiátricos de ansiedade ou depressão.
- Experiência e trauma em cirurgia odontológica anterior.

3.3.2 IDATE

O Inventário de Ansiedade Traço-Estado (IDATE) (ANEXO 2) é um questionário autoaplicável constituído de duas partes. Uma avalia o "estado" ansioso e a outra o "traço" de ansiedade do paciente. Este questionário foi criado por Spielberg, Gasuch e Lushene em 1975 (SPIELBERG et al., 1975) e validado para a língua Portuguesa (Biaggio e Natalício, 1979).

Neste trabalho foram utilizadas as duas partes do questionário, que dá o escore do "estado" e "traço" ansioso, aplicado para todos os participantes do estudo. Consiste de 20 itens com afirmações e as respostas dão um escore que varia de 20 a 80. As respostas que podem ser assinaladas são: "não" = 1, "um pouco" = 2, "bastante" = 3 ou "totalmente" = 4. Quanto maior o escore obtido, maior o nível de ansiedade do paciente. Os pesos dos itens são os mesmos da classificação em pontos (de 1 a 4) assinalados pelo paciente, sendo que os itens onde os escores altos indicam alta ansiedade, permanecem com o mesmo peso assinalado e os itens onde os escores altos indicam baixa ansiedade, têm os seus pesos invertidos, assim evitando tendência de resposta por parte do paciente.

3.3.3 QCirDental

Os escores do instrumento QCirDental (ANEXO 3) foram utilizados como variável de desfecho neste estudo. QCirDental se trata de um questionário aplicado logo após a cirurgia dento-alveolar ter sido realizada, tendo como objetivo quantificar os impactos negativos e desconfortos associados ao procedimento cirúrgico no período trans e pós-operatório imediato. O instrumento contém 20 perguntas que devem ser respondidas numa escala de 0 (zero) a 10 (dez), sendo que o valor zero representa nenhum incômodo durante a cirurgia, e o valor dez indica muito incômodo/ incômodo demais/ um absurdo. Portanto, quanto maior o valor obtido, maior o desconforto sentido durante o procedimento e período pós-operatório imediato. O impacto total pode ser medido através da soma geral dos itens ou a soma total dos itens divididos pelo número de perguntas, sendo que, nesse último caso, obtém-se a percepção de desconforto numa escala de 0-10. A entrevista foi realizada imediatamente ao fim da cirurgia, com o objetivo de conhecer a intensidade do desconforto do procedimento cirúrgico, ela foi conduzida por um único pesquisador (GESR), previamente treinado para tal atividade. Nesse momento o cirurgião e seu

auxiliar se ausentaram do local da entrevista, dando oportunidade para que a paciente respondesse com maior sinceridade sobre a sua percepção da cirurgia. Nesse estudo foi utilizado o método de soma total dos itens dividido pelo número de perguntas.

3.4 TÉCNICA CIRÚRGICA

O procedimento cirúrgico foi realizado por seis residentes, sendo dois do primeiro, dois do segundo e dois do terceiro ano, sempre supervisionados por cirurgião sênior. Houve uma padronização da técnica cirúrgica entre os diferentes operadores. Para a técnica anestésica, foi utilizada a mepivacaína a 2% e norepinefrina 1:100.000 (Mepiadre®, DFL, Taquara, RJ, Brasil). Foi realizado mesmo tipo de incisão, de acordo com a posição anatômica do terceiro molar a ser removido. A ferida cirúrgica foi aproximada com fio de nylon 4-0 (Shalon medical®, Nova Suiça, GO, Brasil) em todos os casos. As intervenções cirúrgicas foram realizadas no período da tarde (entre 13:30 e 18:00), em um ambiente com ar-condicionado. Todos os pacientes foram orientados em relação aos cuidados pós-operatórios necessários.

3.5 ANÁLISES MOLECULARES

3.5.1 Avaliação do perfil hormonal

3mL de amostra sanguínea foi coletada por venopunção por uma enfermeira treinada (IML) previamente a remoção do terceiro molar. Cada tubo de ensaio com a amostra de sangue foi identificado com um número para estipular a relação amostra sanguínea – participante e, após 20 minutos a amostra foi centrifugada, em centrifuga de 10.000 rotações por minuto (rpm), durante 10 minutos (Figura 9A). Após essa etapa, o tubo identificado foi acondicionado em um saco zip e imediatamente entregue ao laboratório, em recipiente adequado, caixa térmica e gelo. (Figura 9B). No laboratório 75µm de sangue foram utilizados para análise dos níveis de Estradiol, 60µm para análise dos níveis de FSH e 20µm para análise dos níveis de Progesterona, realizadas com os kits E2 *Bayer Healthcare e PRGE Bayer Healthcare*, respectivamente no laboratório IDC – Champagnat – razão social: laboratórios Hadiak, Curitiba.

O laboratório foi responsável pelo recebimento do sangue coletado, armazenamento, análise das amostras sanguíneas, emissão de laudo referente aos

níveis de Estradiol, FHS e Progesterona contidos na amostra sanguínea e descarte do material biológico.

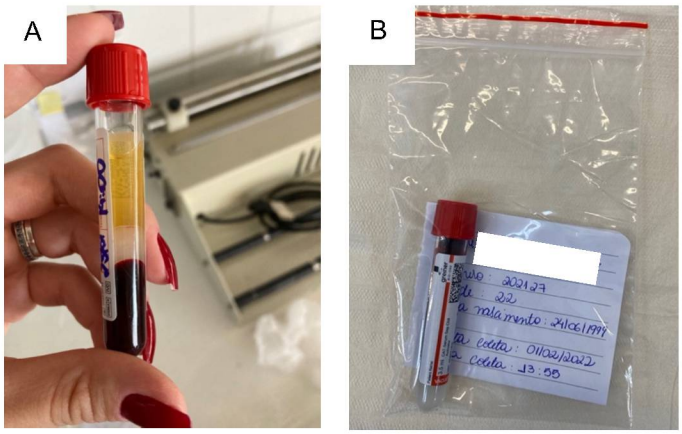


Figura 8A e 8B. Tubo de ensaio com amostra de sangue após centrifugação e amostra pronta para ser transportado ao laboratório.

3.5.2 Coleta do material genético

O DNA foi coletado a partir das células da mucosa, por meio da solução de bochecho. A paciente era instruída a realizar bochecho com 15mL de soro fisiológico pelo período de 60 segundos, após era realizado leve raspagem da mucosa jugal com uma espátula de madeira esterilizada e todo o conteúdo era armazenado em tubo Falcon (KÜCHLER et al., 2011).

3.5.3 Processamento do Material Genético

Onze polimorfismos dos genes *COMT*, *SLC6A4, TRPV1, HTR2A*, *ESR1* e *ESR2* (Tabela 1) foram genotipados pela técnica de reação em cadeia da polimerase (PCR) em tempo real utilizando o sistema *StepOnePlusTM Real-Time PCR* (Thermo Fisher Scientific, Foster City, EUA).

Tabela 1. Características dos polimorfismos estudados.

Gene	Polimorfismos	Localização	Mudança de Base	Frequência alélica mínima /número de indivíduos avaliados
COMT	*rs174675*	chr22(GRCh38.p14)	T/C	T=0,339537 C=0,67110
	rs165656		G/C	C=0,465310 G=0,4500
SLC6A4	*rs3813034*	chr17(GRCh38.p14)	A/C	A=0,17786 C=0,413042
TRPV1	*rs8065080*	chr17:(GRCh38.p14)	T/C	T= 0,32193 C= 0,377096
	rs222747		C/G	C=0,225335 G=0,398
	rs224534		A/G	A=0,357086 G=0,2896
HTR2A	*rs4941573*	chr13:(GRCh38.p14)	G/A	A=0,45849 G=0,364725
	rs6113		G/A	G=0,48765 A=0,420112
ESR1	*rs2234693*	chr6:(GRCh38.p14)	C/T	T=0,497 C=0,462118
ESR2	*rs4986938*	chr14: (GRCh38.p14)	C/T	C=0,410 T=0,312044
	rs126049		C/T	C=0,458079 T=0,38

Disponível em: https://www.ncbi.nlm.nih.gov/snp.

3.5.3.1 Extração do DNA

Foi realizado descongelamento total das amostras e pipetado o conteúdo de 10μL de proteinase K (20mg/mL) em cada tubo de extração. Os tubos Falcon foram mantidos em máquina eletrônica de banho-maria na temperatura de 65°C pelo período de 12 a 24 horas. Após esse período, os tubos foram delicadamente agitados para evitar a formação de bolhas e o sobrenadante foi vertido para tubos de 2mL (Eppendorfs®, Merck KGaA, Darmstadt, Alemanha), na sequência 500μL de acetato de amônio (8M em 1mM EDTA) foi pipetado ao tubo de 2mL e o conteúdo foi deixado em temperatura ambiente (Figura 9A). Os tubos de 2 mL foram mantidos em agitação em vórtex, pelo período de 5 segundos para homogeneização do conteúdo e após, foram centrifugados pelo período de 16 minutos com 13000 rpm, em centrifuga Daiki® (Figura 9B). O sobrenadante foi imediatamente dividido em dois tubos de 1,5mL e o pallet descartado. 540μL de isopropanol foi pipetado em cada tubo e o conteúdo foi centrifugado pelo período de 7 minutos com 13000 rpm (Figura 9C). O

isopropanol foi descartado e 1mL de etanol 70% foi pipetado aos tubos de 1,5mL (Figura 9D), seguido da centrifugação do conteúdo pelo período de 7 minutos com 13000 rpm. O etanol 70% foi descartado e os tubos foram posicionados em estantes para secagem em temperatura ambiente, durante 4 horas (Figura 9E). Por fim, foi adicionado o conteúdo de 50µl de TE (TRIS 10mM; EDTA 1 mM; pH 7,76) (Figura 9F) em cada tubo e esses foram estocados em freezer -20ºC (AIDAR, 2007).

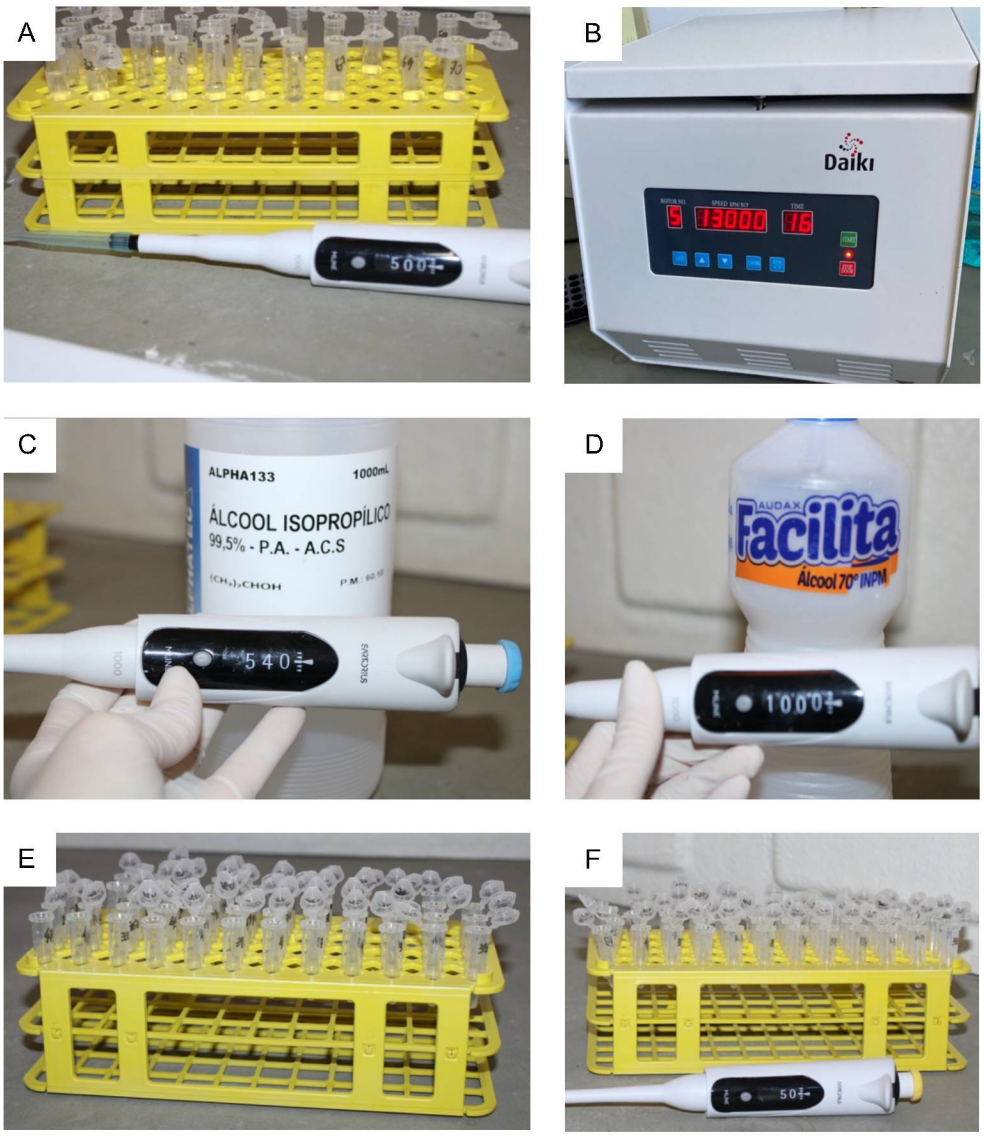


Figura 9. A. Pipetado 500µL de acetato de amônio aos tubos de 2mL B. Protocolo de centrifugação das amostras. C. Pipetado 540µL de isopropanol. D. Pipetado 1mL de álcool 70%. E. Protocolo de secagem. F. Pipetado 50µL de TE para posterior armazenamento das amostras.

3.5.3.2 Genotipagem

Após protocolo de extração do DNA, as amostras foram descongeladas e a concentração de DNA foi dosada por espectrofotômetro *Nanodrop 2000* ThermoScientific™ (Figura 11), a fim de determinar o protocolo de diluição a ser utilizado antes da genotipagem para padronização da concentração de DNA em 20ng/μL. Para a dosagem das amostras foi selecionada a opção para avaliação de ácidos nucleicos. Após a lavagem com água Miliq e realizada a leitura do "branco" com 1μL da solução tampão de eluição em que as amostras foram armazenadas, foi realizada secagem do sensor com o auxílio de lenço de papel para absorção do líquido. Dessa forma, o equipamento estava preparado para realizar as dosagens. Após centrifugar (spin 500 rpm) as amostras de DNA pelo período de 30 segundos, 1μL do DNA foi pipetado no sensor para leitura – esse passo foi repetido para todas as amostras incluídas no estudo.

Figura 10 – Espectrofotômetro Nanodrop 2000 ThermoScientific™.

Em uma *workstation* (cabine com esterilização de luz ultravioleta), foram pipetadas as quantidades totais previamente calculadas de sonda e *MasterMix* (appliedbiosystems TaqMan™) em um único tubo de 1,5mL (Tabela 2). O conteúdo passou por centrifugação pelo período de 30 segundos (spin 500 rpm). Na sequência, em uma placa de 96 poços de 0,1mL (MicroAmp® Fast Optical 96 Well-appliedbiosystems TaqMan™) foi distribuído em cada poço 1,6μL da solução preparada do mix. Um bloco refrigerado foi utilizado para conservar os reagentes

durante o preparo da placa. Para a adição de 1,7 μL de DNA em cada um dos poços da placa, foi utilizada pipeta multicanal, nesse passo a placa e as amostras de DNA ficavam dispostas na mesma conformação (Figura 12A e 12B). Após, o *optical adhesive film* (MicroAmp™ Applied biosystems) foi utilizado para vedar a placa e ela foi levada para centrifugação (spin 3700 rpm) (centrifuga 5810R eppendorf®). No software do equipamento QuantStudio 5 appliedbiosystems®, um novo experimento foi criado, nomeando cada uma das amostras conforme foram montadas na placa, além de inserir o negativo. Informações referentes ao polimorfismo e o gene avaliado eram adicionados ao software. A placa foi encaixada no equipamento conforme a orientação alfabética e a corrida iniciada, utilizando o programa de termociclagem.

Tabela 2. Protocolo de genotipagem adotado no estudo.

	Quantidade para uma amostra	**Quantidade para 96 amostras**
DNA (20 ng/μL)	1,7 μL	-
Marcadores	0,075 μL	0,075x96= 7,2 μL
MasterMix	1,5 μL	1,5x96= 144 μL

Figura 11. A. Disposição da placa para genotipagem, placa de diluição do DNA. B. ponteira multicanal.

3.6 Análise Estatística

Os dados foram analisados através do software Statistical Packger for Social Science (SPSS; versão 25, IBM Corp. Armonk, EUA). Todas as análises inferenciais consideraram nível de significância quando $p< 0,05$. A variável dependente foi o QCirDental, que foi associado com variáveis individuais, relacionadas a saúde feminina, cirúrgicas, anatômicas, radiográficas, relacionadas a ansiedade e genética. O QCirDental apresentou distribuição não paramétrica conforme teste de Kolmogorov-Smirnov, portanto os dados foram representados por mediana, mínimo e máximo. A associação entre o QCirDental e as variáveis independentes foi analisada pelo teste U de Mann-Whitney ou teste de Kruskal Wallis quando havia mais de dois grupos. As

variáveis: idade (≥ 24 ou <24 anos), IMC (≤ 24,9 ou ≥ 25), tempo de cirurgia (> 46 minutos ou ≤ 46 minutos) e número de dentes extraídos (≤ 2 dentes e > 2 dentes) foram dicotomizadas pelas suas respectivas medianas. As distribuições genotípicas foram avaliadas em modelo aditivo, dominante e recessivo para os genes *COMT, SLC6A4, TRPV1, HTR2A e ESR2*. O equilíbrio de Hardy-Weinberg foi avaliado pelo teste Qui-quadrado.

4. ARTIGO 1

EFFECT OF DIFFERENT FACTORS ON WOMEN PERCEPTION OF SURGICAL DISCOMFORT IN THIRD MOLAR SURGERY

ABSTRACT

The aim of this study was to evaluate patient perception of surgical discomfort in third molar surgery and the association with individual, related to women's health, surgical, anatomical, radiographic, and related to anxiety variables. This cross-sectional observational study was carried out on 200 women aged between 18 and 45 years at the Federal University of Paraná in two years. The intensity of surgical discomfort was assessed using the QCirDental questionnaire. Data on individual, women's health, surgical, anatomical and radiographic procedures were also cataloged. Serum levels of progesterone, estradiol, and follicle-stimulating hormone were obtained from blood collection. The anxiety was assessed by the IDATE TRAIT and STATE questionnaire. The data were submitted to statistical analysis with a significance level of 5%. Women with a high body mass index ($p= 0.042$), follicular phase of the menstrual cycle ($p= 0.045$), fewer children ($p= 0.047$), a longer duration of the surgical procedure ($p= 0.012$), traumatic experience in dental surgery ($p= 0.021$), the use of medication for anxiety and depression ($p= 0.016$), and high trait of anxiety ($p= 0.001$) were variables associated with a higher perception of discomfort during tooth extraction. Our findings reinforce that various factors are associated with the perception of discomfort, suggesting the adoption of an individualized model for pai n and discomfort control.

Keywords: Third molars surgery; Menstrual cycle; Patient perception; Anxiety.

INTRODUCTION

The removal of third molars is one of the most performed oral surgery procedures [1]. Most studies about third molars surgery have focused on investigating clinical and radiographic factors that predict the difficulty of tooth extraction or relate to major postoperative complications [2-5]. Few studies in dental surgery have focused on evaluating the patient's perception of the procedure [6-8]. This is an important characteristic because it translates into a viable alternative for assessing the quality of care and services offered, thus providing conditions to recognize and identify more vulnerable individuals to better guide the overall set of preventive and protective actions for patients [7].

The literature proposes a biopsychosocial model that encompasses individual differences for the study of pain [9]. This model postulates that the experience of pain is influenced by complex and dynamic interactions among multiple biological, psychological, and social factors. It is believed that gender, ethnicity, age, medical history, genetics, and psychosocial characteristics influence the painful experience [9].

The menstrual cycle is a biological phenomenon that occurs in healthy women and has a cyclical nature resulting from variations in hormonal concentrations secreted by the hypothalamic-pituitary-gonadal axis [10], lasts approximately 28 days and is subdivided into three phases: follicular, ovulatory, and luteal [11]. In the early follicular phase, the steroid concentrations are low, and in the late follicular phase, estradiol is at its highest levels, and progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) have low concentrations. During ovulation, LH and FSH peak, and in the luteal phase, estradiol and progesterone are at elevated levels [11].

The monthly menstrual cycle causes normative changes in female physiological functioning [12] and can lead to significant alterations in the emotional, cognitive, and behavioral functioning of individuals sensitive to hormones [13]. Knowledge about the menstrual cycle and its physiological mechanism is of great importance for understanding the various biological changes that occur in each phase of the cycle and have a global impact on the female body [14]. Women exhibit higher sensitivity and lower pain tolerance, as well as greater painful somatization, compared to men [15-17]. The literature investigates the role of sex hormones in pain threshold in women [18-23]. There is evidence that the intensity of pain symptoms in women with different disorders fluctuates according to the menstrual cycle phase [24,25]. To our knowledge, this is the first study that investigates the influence of menstrual cycle phases on the perception of discomfort during the removal of third molars.

The real impact of issues related to surgical technique on the perception of discomfort during tooth removal is not yet fully understood. There is evidence suggesting that surgical and radiographic variables do not influence this perception [8]. However, other studies have reported that the surgeon's experience, procedure duration [26], the need for anesthesia supplementation, and the use of a flap [7] are factors associated with a higher perception of discomfort during tooth removal.

Psychological conditions play a significant role in pain perception. Studies that induced experimental acute pain in depressive patients found a lower pain threshold compared to non-depressive individuals [27-29]. Regarding anxiety, a study demonstrated a positive correlation between anxiety and acute pain, where higher anxiety scores before surgery were associated with worse perceived postoperative pain [30]. This study also showed that preoperative anxiety predicts postoperative anxiety [30], a finding also observed in other studies [31-33].

In this study, we hypothesized that surgical discomfort of the patient is a multifactorial characteristic. The knowledge pertaining to factors associated with surgical discomfort of the patient will enable the provision of personalized treatment in dental practice. Therefore, the aim of this study was to evaluate the perception of discomfort during the removal of third molars and associate it with the individual, women's health, surgical, anatomical, radiographic, and anxiety variables.

METHODOLOGY

Study design and sample

This observational cross-sectional study was evaluated and approved by the local ethics committee (43894621.3.0000.0102) and was performed in accordance with the principles of the Helsinki Declaration and the STROBE guidelines for conducting observational studies [34]. The study was conducted from 2021 August to August 2023. The sample comprised 200 women from the Oral and Maxillofacial Surgery Department scheduled for third molar extraction surgery who accepted to participate in this research.

The inclusion criteria were: female, aged between 18 and 45 years, undergoing third molar removal at the Oral and Maxillofacial surgery (OMS) service of UFPR, and agreeing to participate in the study. The exclusion criteria were pregnant women, breastfeeding, hormone replacement therapies, and menopause.

It is important to emphasize that in the Surgery Department, the patients that present infection and/or inflammation are not submitted to the procedure. Besides, there is not a medication protocol to control anxiety or

decrease the signs of inflammation preoperatively. Therefore, the participants did not use any medication prior to the surgery.

The sample size was calculated considering the following parameters: an estimated population of 400 women who undergo third molars extractions in 2 years at the University, an anticipated frequency of 50%, a confidence limit of 5%, and a design effect of 1. Using these parameters, the calculations resulted in a sample size of 197 women (www.openepi.com/samplesize) [36].

Briefly, women scheduled for the extraction of third molars at the OMS service of UFPR were invited to participate in the study. Those who accepted were taken to a separate room where they filled out a clinical form related to individual and women's health variables and the IDATE TRAIT and IDATE STATE questionnaires. Following this, the participant was taken for dental extraction, during which the researchers collected surgical, anatomical, and radiographic variables. At the end of the surgery, the participant answered the QCirDental questionnaire in a separate room (Figure 1).

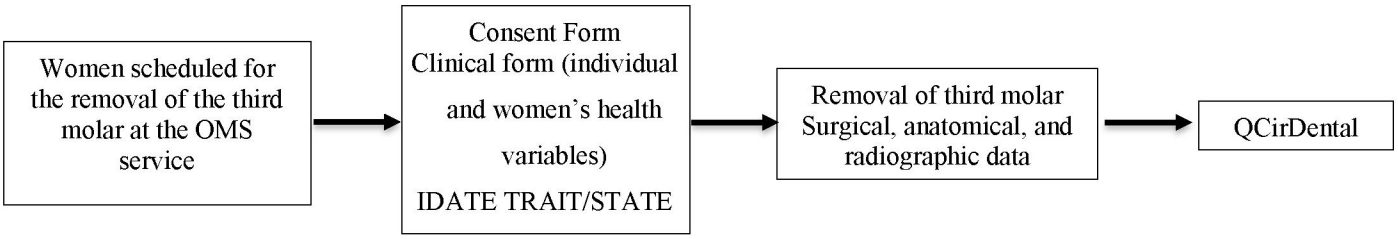


Figure 1. Flowchart illustrating the study stages.

Individual variables evaluated

Individual characteristics such as age, (white, black, yellow and brown) and body mass index (BMI, calculated by dividing weight (in kilograms) by height (in meters) squared were recorded. Based on the recommendations of the World Health Organization, women were classified as ≤ 24.9 (underweight and normal weight) or ≥ 25 (overweight and obese).

Variables related to women's health

Variables related to women's health (menstrual cycle phase, Concentrations of progesterone, estradiol, and FSH, use of contraceptive methods, number of children, presence of chronic pain, presence of orofacial pain) were recorded.

To determine the phase of the menstrual cycle, the following protocol was adopted:

The most common menstrual cycle duration is 28 days; however, variations can occur, ranging from 21 to 35 days. Therefore, adopting a standardization of 28 days for all women may compromise the reliability of the data. Since the goal was to determine the phase of the menstrual cycle each woman was in on the day of tooth extraction, this data was individualized. To obtain this information, participants were asked to provide the average duration of their menstrual cycles, as well as the first and last day of menstruation in the last cycle. Thus, the following convention was adopted to determine the phase in which the participant was at the time of surgery.

The follicular phase was considered to start on the 1st day and end between the 8th day (for 21-day cycles), the 15th day (for 28-day cycles), and the 21st day (for 35-day cycles). To determine the ovulatory phase, the

countdown method was adopted, with days -15 to -12 before the start of menstruation. The luteal phase has less variability in duration, so 14 days were considered after the end of the ovulatory phase [13].

In each phase of the menstrual cycle, there is a variation in the hormonal pattern. To reduce recall bias from the participants, when we reached the cycle phase based on the report, it was confirmed by the hormonal levels of estradiol (E2), progesterone (P4), and FSH, as shown in the Chart 1.

Chart 1. Average hormonal levels considered in each phase of the menstrual cycle.

FOLLICULAR PHASE	OVULATORY PHASE	LUTEAL PHASE
Beginning • P4: ≅ 0.5 ng/mL • Estradiol: ≅ 40 pg/mL • FSH: ≅ 10 a 20 mUI/mL Middle • E2: ≅ 200 pg/mL • P4: ≅ 0.5 ng/mL	• FSH: ≅ 40 mUI/ml • Slight increase in P4 and drop in E2	Beginning • High levels of P4 Middle • E2: ≅ 120 pg/mL

Note: P4: progesterone, E2: estradiol.

Evaluation of Serum Hormonal Profile

3 ml of blood sample was collected by venipuncture by a trained nurse (IML) prior to the removal of the third molar. Each test tube with the blood sample was identified with a number to establish the sample-blood participant relationship, and after 20 minutes, the sample was centrifuged, following this protocol: centrifuge at 1,300 rotations per minute (rpm) for 10 minutes. After this step, the identified tube was placed in a ziplock bag and immediately delivered to the IDC laboratory – Champagnat – legal name: Hadiak laboratory, Curitiba. In the laboratory, the serum was extracted and analyzed. Total serum concentrations were evaluated using a microparticle enzyme immunoassay (MEIA) technology for the sex steroid hormones estradiol, progesterone, and FSH, through the E2 Bayer Healthcare and PRGE Bayer Healthcare kits. This analysis protocol was previously described in the literature [36,37].

Surgical, anatomical and radiographic variables evaluated

The surgical variables were as follows: resident's training stage (~~R1, R2 or R3~~ – categorized according to the year of training in OMS service); surgery duration (in minutes from the arrival in the operating room until the end of the surgical procedure); number of teeth removed (≤ 2 or >2, as in some situations, the four third molars were not removed in the same procedure, but in two periods, two teeth per period); osteotomy procedure (yes or no); and toothsection procedure (yes or no).

Regarding anatomical variables, we assessed root curvature (small or large), root divergence (small or large), and the proportion of crown size to root size (crown the same size as the root, crown larger than the root, crown smaller than the root). The third molars were classified using panoramic radiographs according to Winter's classification [38] by a single trained researcher (GESR), previously trained by a senior researcher (RS). The Winter's classification was used to determine the long axis angulation of the impacted third molar relative to the

long axis of the adjacent second molar, classifying the third molar as having mesioangular, vertical, horizontal, and distoangular impactions.

Anxiety-related variables assessed

Variables related to anxiety (trait and stait of anxiety, previous dental removal, traumatic experience in dental surgery and use of anxiety/depression medication) were recorded. To determine the levels of anxiety, we used IDATE questionnaire. The variable anxiety was categorized (20-38: low anxiety; 39-42: normal and 43-80: high anxiety).

IDATE questionnaire

The anxiety levels of the participants were assessed before the removal of the third molar. The State-Trait Anxiety Inventory (STAI) was used as the evaluation tool, with the version validated and translated into Brazilian Portuguese [39]. The instrument consists of 20 objective questions, from which the participant must indicate how 'he generally feels in the last 6 months' (Trait) or how he is feeling at the moment (State). Response options were categorized as: almost never, sometimes, frequently, and almost always. Based on the responses obtained, a specific scoring scale is derived. The total score ranges from 20 to 80, with a higher score indicating higher anxiety.

Surgical Technique

The surgical procedure was performed by residents in the first, second, or third year. For the anesthetic technique, 2% mepivacaine with 1:100,000 norepinephrine (Mepiadre®, DFL, Taquara, RJ, Brazil) was used. The surgical wound was closed with 4-0 nylon suture in all cases (Shalon medical®, Nova Suiça, Goiânia, Brazil). Surgical interventions were carried out in the afternoon (between 13:30 and 18:00), in an air-conditioned environment.

QCirDental questionnaire

QCirDental is a questionnaire developed and validated for the Brazilian Portuguese language to quantify the negative impact and discomfort associated with the surgical procedure [7]. Immediately after the surgery, participants completed the questionnaire in a separate room with the presence of the researcher only, who was previously trained to use the QCirDental questionnaire. The questionnaire consists of 20 items about the discomfort during the operative and the immediate postoperative periods answered on a scale from 0 (no discomfort) to 10 (highest level of discomfort). The degree of the effect (represented in this study as intensity of discomfort) is the sum of the scores of individual questions divided by the number of questions.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (IBM SPSS for Apple OS, version 25, IBM Corp. Armonk, USA). All inferential analyses considered a significance level of $p \leq 0.05$. The dependent variable was QCirDental, which was associated with the following independent variables: age, height, body mass index (BMI), variables related to female health, surgical procedure-related variables, anatomical and radiographic variables, and variables related to anxiety. QCirDental had a non-parametric distribution according

to the Kolmogorov-Smirnov test; therefore, the data were represented by median, minimum, and maximum values. The association between QCirDental and independent variables was analyzed using the Mann-Whitney U test or Kruskal-Wallis test when there were more than two groups. The variables: age (≥ 24 or < 24 years), BMI (≤ 24.9 or ≥ 25), surgery time (> 46 minutes or ≤ 46 minutes), and number of teeth extracted (≤ 2 teeth and > 2 teeth) were dichotomized based on their respective medians. The variable number of children was dichotomized in (≤ 1 or ≥ 2). The variable anxiety was categorized as described in the literature [39,40] (20-38: low anxiety; 39-42: normal and 43-80: high anxiety). Menstrual cycle phase was categorized into follicular, ovulatory, and luteal. Hormonal levels were categorized following the literature, dichotomizing the levels of estradiol in: (>51 pg/mL or ≤51 pg/mL) [18] and the levels of progesterone in: (> 1.0 ng/mL or ≤ 1.0 ng/mL) [39]. FSH levels were dichotomized by their respective median in: (≤ 4.87 or >4.87).

Cegamento – limitações?

RESULTS

Out of the total number of women approached to participate in the study, 35 were not included. In total, 207 participants were included. During the process, 7 women were excluded, all of whom did not undergo the surgical procedure due to systemic alterations that prevented surgery. Therefore, a sample of 200 women was obtained, totaling 416 extracted third molars (Figure 2). The median age of the sample was 24 years (ranging from 18 to 45), and the median BMI was 23.1 (ranging from 16 to 41.3). Regarding race, 77.4% were white (n= 154), 5.5% were black (n= 11), 0.5% were yellow (n= 1), and 16.1% were brown (n= 32).

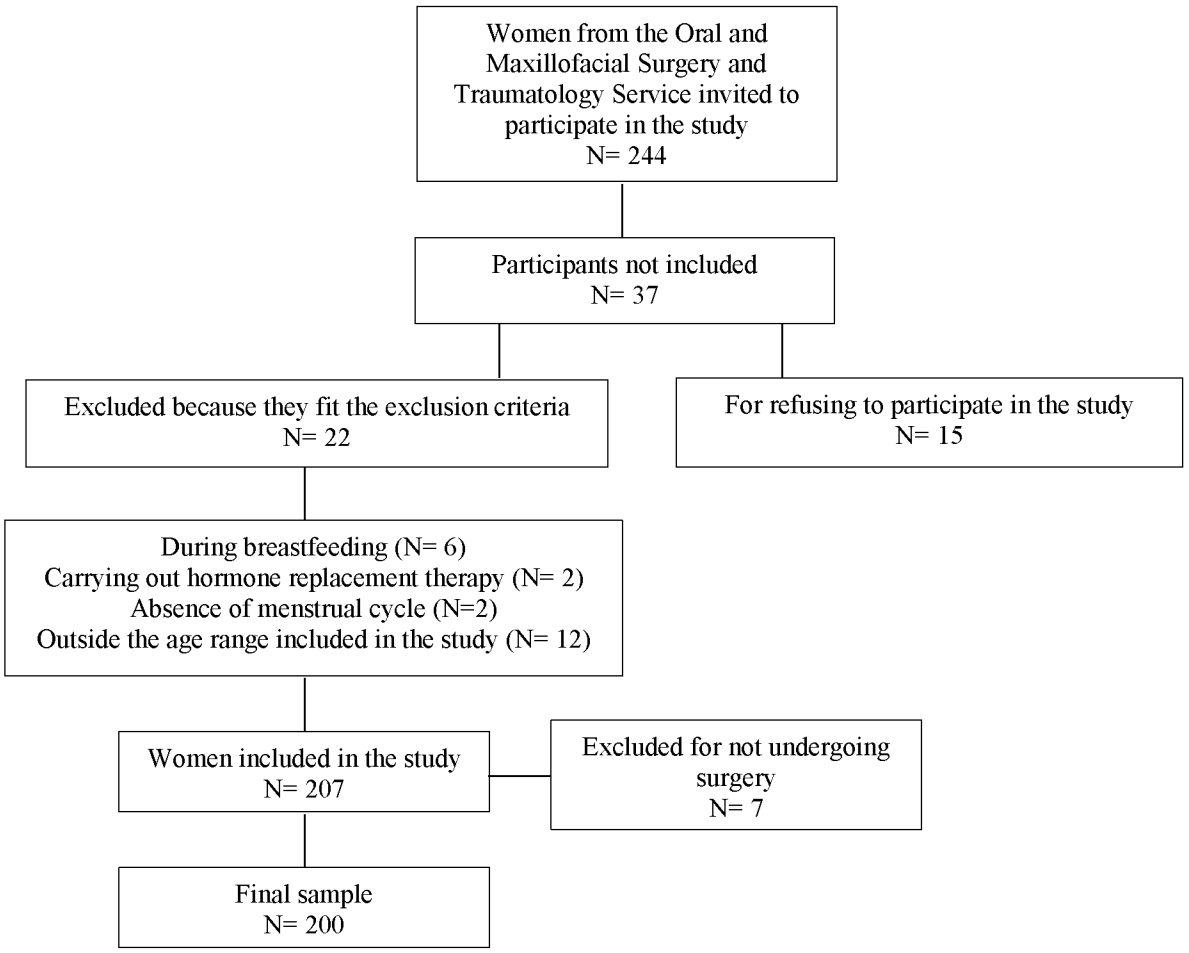


Figure 2. Flowchart illustrating the composition of the studied sample.

Only 2.5% of the participants in this study did not report discomfort on the 20 questions of the QCirDental instrument. The median score found for the instrument was 1.50 (ranging from 0 to 26). The association of QCirDental with individual variables is presented in Table 2. Patients classified as overweight/obese based on BMI reported higher discomfort levels than those with normal/underweight BMI (*p= 0.032*). These data can be further observed in Table 1.

Table 1. Median (min and max) scores for surgical discomfort according to individual characteristics of the sample.

Individual variables			Surgical Discomfort Med (min – max)	p- value
Age (years)	≥ 24	N (114)	1.50 (0 – 8.9)	*0.366*
	< 24	N (86)	1.40 (0 – 26)	
BMI	≤ 24.9	N (127)	1.45 (0 – 5.3)	***0.042***
	≥ 25	N (70)	1.70 (0 – 26)	
Race	White	N (154)	1.50 (0 – 26)	
	Black	N (11)	1.40 (0 – 3.8)	*0.712*
	Yellow	N (1)	-	
	Brown	N (31)	1.40 (0 – 8.9)	

Mann-Whitney U test or Kruskal Wallis with significance level of 0.05. Bold values indicate statistical significance. Med: median; Min: minimum; Max: maximum; BMI: body mass index.

Regarding the phases of the menstrual cycle, 48.9% (n= 89) were in the follicular phase, 6.6% (n= 12) were in the ovulatory phase, and 44.5% (n= 81) were in the luteal phase. There was an association between the menstrual cycle phase and discomfort perception, with participants in the follicular phase significantly reporting more discomfort than those in the luteal phase (*p= 0.033*). Regarding the levels of progesterone, estradiol, and FSH, no statistical associations were found with the levels of surgical discomfort (*p> 0,05*). Being menstruating did not influence discomfort during the removal of third molars (*p= 0.303*). Women who are not mothers have a higher perception of discomfort (*p= 0.007*). Additionally, the greater the number of children, the lower the perception of discomfort during the removal of third molars (*p= 0.008*) These data can be viewed in Table 2.

Table 2. Association between the median (min and max) surgical discomfort scores and variables related to women's health.

Variables related to women's health			Surgical Discomfort Med (min – max)	p-value
Menstrual cycle phase	Follicular	N (89)	1.70 (0 – 14)[a]	
	Ovulatory	N (12)	1.50 (0.2 – 4.9)[ab]	***0.045****
	Luteal	N (81)	1.20 (0 – 8.9)[b]	
Progesterone levels	≤ 1	N (132)	1.47 (0 – 26)	*0.659*
	> 1	N (41)	1.55 (0 – 7.4)	
Estradiol levels	≤ 51	N (91)	1.50 (0 – 26)	*0.973*
	> 51	N (82)	1.47 (0 – 5.6)	
FSH levels	≤ 4.87	N (86)	1.45 (0 – 26)	*0.637*
	< 4.87	N (87)	1.50 (0 – 14)	
Menstruation	Yes	N (29)	1.70 (0.4 – 14)	*0.303*
	No	N (170)	1.50 (0 – 26)	
Oral contraceptive use	Yes	N (58)	1.50 (0.1 – 26)	*0.376*
	No	N (141)	1.50 (0 – 14)	
Injectable contraceptive use	Yes	N (24)	0.97 (0 – 8.9)	*0.052*
	No	N (175)	1.50 (0 – 26)	
Transdermal patch contraceptive use	Yes	N (2)	0.75 (0.7 – 0.8)	*0.259*
	No	N (197)	1.50 (0 – 26)	
Levonorgestrel intrauterine	Yes	N (13)	1.20 (0 – 3.6)	*0.307*
	No	N (186)	1.50 (0 – 26)	
Is a mother	Yes	N (58)	1.35 (0 – 7.4)	***0.007***
	No	N (141)	1.65 (0 – 26)	
Number of children	≤ 1	N (166)	1.55 (0 -26)	***0.008***
	≥ 2	N (33)	1.0 (0 – 5.0)	
Chronic pain	Yes	N (30)	1.50 (0 – 7.4)	*0.685*
	No	N (131)	1.55 (0 – 26)	
Orofacial pain	Yes	N (30)	1.52 (0 – 8.9)	*0.358*
	No	N (169)	1.50 (0 – 26)	

Bold values indicate statistical significance. Med: median; Min: minimum; Max: maximum.
Mann-Whitney U test or Kruskal Wallis with significance level of 0.05. * Means post Mann-Whitney test.

Salientar que foi sempre em um mesmo tempo cirurgico quando mais de um dente foi extraido

The surgical variables associated with discomfort perception are presented in Table 3. Surgical procedures with longer duration were associated with a higher perception of discomfort during the removal of third molars (*p= 0.012*). Regarding the other factors, there was no statistically significant association.

Table 3. Association between discomfort perception during the removal of third molars and surgical variables.

Surgical variables			Surgical Discomfort Med (min – max)	*p-value*
Resident's training stage	R1	N (42)	1.40 (0 – 4.9)	
	R2	N (66)	1.87 (0 – 14)	*0.062*
	R3	N (68)	1.45 (0 – 26)	
Surgery duration (minutes)	≤ 46	N (92)	1.40 (0 – 26)	***0.012***
	> 46	N (91)	1.85 (0 – 8.9)	
Number of extracted teeth	> 2	N (167)	1.50 (0 – 8.9)	*0.681*
	≤ 2	N (32)	1.40 (0 – 26)	
Surgical Technique - Osteotomy Procedure				
Tooth 18	Yes	N (5)	2.10 (1.2 – 3.7)	*0.093*
	No	N (105)	1.45 (0 – 26)	
Tooth 28	Yes	N (10)	2.10 (0.4 – 14)	*0.188*
	No	N (87)	1.55 (0.1 – 6.0)	
Tooth 38	Yes	N (55)	1.70 (0 – 14)	*0.124*
	No	N (43)	2.60 (0.1 – 7.4)	
Tooth 48	Yes	N (56)	1.35 (0 – 5.0)	*0.863*
	No	N (53)	1.50 (0 – 26)	
Surgical Technique - Odontosection Procedure				
Tooth 18	Yes	N (1)	-	*0.309*
	No	N (109)	1.45 (0 – 26)	
Tooth 28	Yes	N (4)	1.57 (1.5 – 2.0)	*0.842*
	No	N (94)	1.55 (0.1 – 4)	
Tooth 38	Yes	N (45)	2.0 (0 – 8.9)	*0.094*
	No	N (53)	1.25 (0,1 – 14)	
Tooth 48	Yes	N (51)	1.55 (0 – 4.5)	*0.421*
	No	N (58)	1.47 (0 – 26)	

Bold values indicate statistical significance.
Mann-Whitney U test or Kruskal Wallis with significance level of 0.05.

Regarding the anatomical and radiographic characteristics of the third molars, in the third molars with a higher level of root curvature, there was a higher median of surgical discomfort, with a significant association between these variables in tooth 18 (*p= 0.023*). An association was also found between higher levels of root divergence and the perception of discomfort during dental removal for tooth 18 (*p= 0.011*). These data can be viewed in Table 4.

Table 4. Association between the perception of discomfort during the removal of third molars and anatomical and radiographic characteristics.

Anatomical and radiographic variables			Surgical Discomfort Med (min – max)	p-value
Root curvature				
Tooth 18	Small	N (80)	1.22 (0 – 26)	***0.023***
	Large	N (28)	1.92 (0.2 – 3.8)	
Tooth 28	Small	N (86)	1.55 (0.1 – 14)	*0.837*
	Large	N (12)	1.57 (0.3 – 4.5)	
Tooth 38	Small	N (75)	1.50 (0 – 14)	*0.979*
	Large	N (21)	1.70 (0.2 – 3.8)	
Tooth 48	Small	N (75)	1.45 (0 – 26)	*0.452*
	Large	N (30)	1.70 (0.2 – 5.3)	
Root divergence				
Tooth 18	Small	N (79)	1.25 (0 – 26)	***0.011***
	Large	N (28)	2.0 (0.2 – 5.6)	
Tooth 28	Small	N (81)	1.55 (0.1 – 14)	*0.904*
	Large	N (15)	1.45 (0.1 – 6.0)	
Tooth 38	Small	N (82)	1.55 (0 – 14)	*0.745*
	Large	N (13)	1.10 (0.4 – 3.8)	
Tooth 48	Small	N (79)	1.45 (0 – 26)	*0.494*
	Large	N (26)	1.70 (0.2 – 5.3)	
Crown-root ratio				
Tooth 18	Crown > root	N (11)	1.0 (0.1 – 4.4)	
	Crown = root	N (22)	1.35 (0.1 – 2.8)	*0.206*
	Crown < root	N (75)	1.65 (0 – 26)	
Tooth 28	Crown > root	N (9)	2.5 (0.9 – 4.4)	
	Crown = root	N (21)	1.55 (0.1 – 4.9)	*0.091*
	Crown < root	N (69)	1.50 (0.1 – 14)	
Tooth 38	Crown > root	N (11)	2.5 (0.4 – 6.0)	
	Crown = root	N (27)	2.0 (0 – 8.9)	*0.087*
	Crown < root	N (57)	1.40 (0.1 – 14)	
Tooth 48	Crown > root	N (14)	1.32 (0.4 – 4.5)	
	Crown = root	N (27)	1.65 (0.1 – 8.9)	*0.949*
	Crown < root	N (65)	1.50 (0 – 26)	
Radiographic classification of Winter				
Tooth 18	Mesioangular	N (24)	1.82 (0 - 26)	
	Horizontal	N (0)	-	*0.213*
	Vertical	N (56)	1.22 (0 – 5.6)	
	Distoangular	N (30)	1.52 (0.1 – 4.4)	
Tooth 28	Mesioangular	N (12)	1.32 (0.3 – 3.8)	
	Horizontal	N (1)	-	*0.069*
	Vertical	N (51)	1.40 (0.1 – 6.0)	
	Distoangular	N (32)	2.12 (0.1 – 7.4)	
Tooth 38	Mesioangular	N (30)	1.77 (0 – 5.7)	
	Horizontal	N (19)	1.85 (0.3 – 8.9)	*0.581*
	Vertical	N (38)	1.40 (0.1 – 7.4)	
	Distoangular	N (8)	1.52 (0.3 – 2.1)	
Tooth 48	Mesioangular	N (48)	1.47 (0 – 4.5)	
	Horizontal	N (13)	0.90 (0 – 2.9)	*0.598*
	Vertical	N (37)	1.55 (0.1 – 26)	
	Distoangular	N (11)	1.50 (0.5 – 4.1)	

Bold values indicate statistical significance.
Mann-Whitney U test or Kruskal Wallis with significance level of 0.05.
*> = bigger; = equal; < = smaller.

A statistical association was found between anxiety and the perception of surgical discomfort (*p= 0.002*). It was observed that women with a high trait of anxiety had a greater perception of discomfort during the removal of third molars, when compared to women with a normal anxiety score *(p= 0.001*). Associations with the state of anxiety could not be assessed since all women in the sample exhibited high levels of anxiety. There was no association between prior exposure to dental extraction and the discomfort perceived by the patient during the removal of third molars (*p= 0.784*). On the other hand, participants who reported having had a traumatic experience in past dental surgeries were associated with higher discomfort perception scores during the removal of third molars (*p= 0.021*). Another factor evaluated was the use of medication for anxiety or depression, and women using these medications were associated with higher QCirDental scores (*p= 0.016*) (Table 5).

Table 5. Association between the median (min and max) surgical discomfort scores and variables related to anxiety.

Variables related to anxiety			Surgical Discomfort Med (min – max)	p-value
IDATE Trait	Low anxiety (20-38)	N (16)	1.0 (0 – 14)[ab]	***0.002****
	Normal anxiety (39-42)	N (27)	1.20 (0 – 2.8)[a]	
	High anxiety (43-80)	N (157)	1.55 (0 – 26)[b]	
IDATE State	Low anxiety (20-38)	N (0)	-	-
	Normal anxiety (39-42)	N (0)	-	
	Hogh anxiety (43-80)	N (200)	1.5 (0 – 26)	
Previous dental removal	Yes	N (110)	1.45 (0 – 26)	*0.784*
	No	N (87)	1.50 (0 – 7.4)	
Traumatic experience in dental surgery	Yes	N (34)	2.10 (0.2 – 26)	***0.021***
	No	N (164)	1.40 (0 – 14)	
Use of anxiety/depression medication	Yes	N (37)	1.9 (0 – 8.9)	***0.016***
	No	N (160)	1.4 (0 – 26)	

Bold values indicate statistical significance. Med: median; Min: minimum; Max: maximum.
Mann-Whitney U test or Kruskal Wallis with significance level of 0.05. * Means post Mann-Whitney test.

DISCUSSION

The objective of this study is to elucidate the main variables associated with the perception of discomfort during the removal of third molars. Only 2.5% of the participants did not report any discomfort during the surgery, which differs from what is reported in the literature, where 19% of participants were found to be free from the perception of discomfort during the removal of third molars [8]. We believe that this difference occurred because, in the present study, we included only women. This highlights the importance of delving into the understanding of the difference in pain perception between genders.

About the individual variables studied, we found an association between BMI and the perception of discomfort during the removal of third molars, where individuals with overweight or obesity reported higher discomfort. Various medical studies demonstrate the association between BMI and worse surgical outcomes [41,42], such as evidence showing that increased BMI is associated with significantly worse perioperative outcomes in spinal surgeries [43]. Additionally, a study with obese parturient showed that increased BMI is associated with a higher rate of surgical wound complications. Furthermore, a study with individuals undergoing

surgical treatment for colon cancer found evidence that BMI was increasingly associated with wound-related complications, linking obesity to an increasing risk of surgical complications [44]. Thus, it is essential to emphasize that while the surgical community strives to improve the quality of care, patient-controlled factors will play an essential role in this improvement. Regarding the variables age and race, we found no significant differences, a result in line with the literature [8].

Women show greater sensitivity and lower pain tolerance, as well as greater painful somatization, when compared to men [15-17]. The mechanisms of pain differentiation between genders are not yet fully elucidated; however, there is evidence that ovarian hormones play an important role in pain modulation [45]. Understanding these mechanisms better would broaden our understanding of why painful disorders are more frequent, severe, and disabling in women than in men. In this regard, we assessed whether the menstrual cycle phase affects women's discomfort perception and found that women in the follicular phase of the menstrual cycle had significantly greater discomfort perception during the removal of third molars. A meta-analysis of 16 studies found that the menstrual cycle has a significant effect on pain perception, with the follicular phase demonstrating higher thresholds than later phases for pressure stimulation, cold pain, thermal stimulation, and ischemic muscle pain [46]. However, previous publications have shown that pain perception may be higher in the luteal phase, as demonstrated in a study that subjected 15 volunteers to a 4 mm incision on the forearm, showing that in the luteal phase, women exhibited higher pain sensitivity and hyperalgesia [23]. Another study examining the pain level of propofol injection found that women in the luteal phase significantly experienced higher pain levels [47]. The literature is still controversial regarding the elucidation of the role of the menstrual cycle phase in pain perception, so further research on the topic is necessary.

The literature supports the existence of pregnancy-induced analgesia, explained by a series of physiological changes that occur in the female body. Pseudopregnancy, where a hormonal environment like that of pregnancy occurs but without the presence of an embryo, supports the idea that analgesia arises, at least in part, secondary to the exponential increase in sex steroids hormones, estrogen, and progesterone [48]. Increases in estrogen and progesterone levels occur monthly in healthy women during the luteal phase [49], so there is believed to be luteal analgesia. When analyzing the hormonal levels of progesterone, estradiol, and FSH individually with the perception of discomfort, we found no statistical associations. This suggests minimal interference of sex hormones in the patient's perception of discomfort, further supporting the biopsychosocial model for the study of pain [9]. Although the menstrual cycle and its effects on the body have been studied for years, there is a lack of standardized guidelines in the design of studies and in determining cycle phases, which we attribute to the many differences found in previous studies [13].

Having children was associated with a lower perception of discomfort, and the more children a woman had, the lower the reported discomfort during the removal of third molars. It is known that living with children can contribute to good health through close social and emotional relationships, as well as mechanisms for structuring daily life, social control, and the meaning of life [50]. On the other hand, we hypothesize that mothers may have more concerns about their children and a different sense of responsibility, which can affect their perception.

About the evaluated surgical variables, we found an association between longer surgeries and a greater perception of discomfort. This result differs from what was found by Reis et al., 2020 [8]. However, a previous study indicated an association between time and the complexity of surgery [26]. For us, it seems understandable that more time in the operating room is associated with a greater perception of discomfort because the patient may

feel more tired, anxious, and consequently interpret the discomfort as greater. We believe that we found a different result from the study by Reis et al., 2020, because our sample consisted only of women. Regarding other surgical, anatomical, and radiographic variables, no significant associations were found. This result confirms what was found previously by Reis et al., 2020. We believe that often we may overestimate the mentioned variables, and perhaps the main outcome is centered on the patient.

In this study, more anxious women also showed a greater perception of discomfort during the removal of third molars, a result like that found by Fardal et al., 2012 [51], where patients underwent periodontal surgery and implant treatments, and the perception of pain was affected by the level of pre-surgical anxiety. The scientific literature has long investigated the influence of anxiety on the patient's experience, yielding very interesting results, such as a study that demonstrated that highly anxious patients expected more pain than they felt during tooth extraction [52]. Additionally, another study conducted with patients undergoing tooth extraction found a correlation between more anxious patients and reports of pain using the visual analog scale (VAS), concluding that preoperative dental anxiety is an important predictor of pain felt by patients during tooth extractions [53]. Nevertheless, patients' anxiety can adversely affect the surgeon's performance, significantly increase the duration of the procedure, recovery time, and the dose of analgesics [54,55]. Therefore, it is important to reduce anxiety before treatment to minimize the perception of pain during the procedure. One study suggests mechanisms that act to decrease anxiety, usually linked to oral health education, such as video demonstration before tooth extraction procedures [56]. Another alternative is the pharmacological modality, using sedation.

In the present study, we found that women who reported traumatic experiences in dental surgeries had a higher perception of discomfort during tooth extraction. This finding is discussed in the literature; a case-control study demonstrated that negative dental experiences in childhood influence dental fear in adulthood [57]. Moreover, the literature has shown that individuals become more fearful as they age and accumulate more negative health-related experiences [58-61]. This variable underscores the importance of patient care in the provision of services. A strategy to reduce the occurrence of trauma in patients is through oral health education. Women who use medication for anxiety or depression also experienced more discomfort during the removal of third molars. The literature points out that depression is an important co-factor in the experience of pain [62], and neuroticism and depression influence pain assessment, suggesting that depressed patients tend to judge recent pain as more intense than that felt previously [63].

Regarding the limitations of this study,-it would be interesting to conduct a split-mouth clinical study where the same woman is operated on one side during the follicular phase and on the other side during the luteal phase of the menstrual cycle to provide more robust evidence of the influence of the menstrual cycle on the perception of discomfort. We understand that the findings in our study are preliminary and should be interpreted with caution, not justifying scheduling dental extraction surgeries targeting specific phases of the menstrual cycle.

Our findings suggest that various factors will interfere with the patient's perception of discomfort, ranging from individual factors such as BMI, menstrual cycle, motherhood, number of children, duration of the surgical procedure, anxiety trait, previous traumatic experience, and the use of medication for anxiety or depression. This reinforces the principles advocated by the biopsychosocial model. Emphasizing the need for individualized treatment, prioritizing the well-being of patients undergoing third molar removal.

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5. ARTIGO 2

EFFECT OF GENETIC POLYMORPHISMS ON WOMEN PERCEPTION OF SURGICAL DISCOMFORT IN THIRD MOLAR SURGERY

ABSTRACT

The aim of this cross-sectional observational study was to associate the perception of discomfort during the removal of third molars with genetic polymorphisms of *COMT*, *SLC6A4*, *TRPV1*, *HTR2A*, *ESR1* and *ESR2 genes*. This study was carried out on 200 women aged between 18 and 45 years at the Federal University of Parana in two years. The intensity of surgical discomfort was assessed using the QCirDental questionnaire. The DNA sample was obtained from cells of the oral mucosa. Eleven markers of the *COMT*, *SLC6A4*, *TRPV1*, *HTR2A*, *ESR1* and *ESR2* genes were genotyped. The data were submitted to statistical analysis with a significance level of 5%. In the additive and dominant model, the TT genotype for the *rs174675* was associated with a greater surgical discomfort ($p= 0.014$) and ($p= 0.006$) respectively. Additionally, in the dominant model, individual with GG genotype for the *rs6113* reported greater surgical discomfort with third molar surgery ($p= 0.038$). Therefore, women of TT genotype for the *rs174675* marker in *COMT* gene and women of GG genotype for *rs6313* in *HTR2A* gene reported greater surgical discomfort associated with third molar surgery.

Keywords: Third molars surgery; Polymorphism genetic; Patient perception.

INTRODUCTION

Surgery for the removal of third molars is a commonly performed procedure in the clinical routine of dentists [1]. The literature has long investigated factors associated with increased morbidity in this procedure to technically prepare professionals to provide the best treatment for their patients [2-4]. However, not all patients respond in the same way to the surgical procedure. Pain perception, the need for analgesic medication [5], and the trauma resulting from the procedure vary from individual to individual. In recent decades, the theory based on the biopsychosocial model has grown to understand individuality in perceptions and individual responses [6]. In this context, the scientific community has increasingly investigated the role of psychological, social, and biological factors in pain response [6].

Various studies seek to understand the role of genetic biomarkers in individual responses, and scientific research still strives to uncover the genetic bases of phenotypes associated with pain perception. Previous studies conducted by this team have shown that genetic polymorphisms are associated with the anxiety levels of patients undergoing third molar extraction and the perception of discomfort during dental removal [7,8]. Knowledge of genetic predisposition offers great potential for the future in individualizing treatments, promoting a profound understanding of everyone's condition [9]. The ultimate value in understanding the genetic determinants of pain will be able to reduce suffering in human populations [10].

In this study, we selected polymorphisms from six different genes for investigation. *The Catechol-O-methyltransferase gene* (*COMT*) plays a crucial role in the degradation of catecholamine transmitters and was chosen due to its associations with schizophrenia [11], treatment-resistant depression [12], anxiety [13], painful conditions [14], and psychotic disorders [1]. The *Solute Carrier Family 6 member 4 gene* (*SLC6A4*), essential for serotonin homeostasis in the central nervous system, was selected for its association with schizophrenia [16] and

The article is standardized according to the Clinical oral investigations standards, available in annex 4 of this work.

The *Transient Receptor Potential Vanilloid Subfamily V Member 1* gene (*TRPV1*) has an important function in detecting harmful chemical and thermal stimuli through a non-selective calcium-permeable cationic channel. It is involved in mediating inflammatory pain and hyperalgesia and has been previously associated with pain sensitivity [18], playing a significant role in cancer-related pain [19]. The *5-hydroxytryptamine 2A receptor gene* (*HTR2A*) encodes one of the serotonin receptors, a neurotransmitter that plays a crucial role in communication between nerve cells. Polymorphisms in *HTR2A* have been associated with obsessive-compulsive disorder [20], depressive disorders, and schizophrenia [21, 22].

The genes for sexual steroid receptors (*ESR1* and *ESR2*) play a crucial role in the regulation of emotions, cognition, and behavior in various brain regions such as the hypothalamus, amygdala, cerebral cortex, hippocampus, and brainstem [23, 24]. Associations have been found between *ESR1* and anxiety [25], neuroticism, psychotism, and irritability [26], and between *ESR2* and depression [27], as well as variations in mood [28].

The hypothesis in our study is that the perception of surgery discomfort can be modulated by genetic polymorphisms associated with pain/discomfort. The aim of this study was to associate the perception of discomfort during the removal of third molars with genetic polymorphisms.

METHODOLOGY

Study design and sample

This observational cross-sectional study was evaluated and approved by the local ethics committee (43894621.3.0000.0102) and was performed in accordance with the principles of the Helsinki Declaration and the STREGA guidelines for conducting observational studies with genetic analysis [29]. The study was conducted from 2021 August to August 2023. The sample comprised 200 women from the Oral and Maxillofacial Surgery Department scheduled for third molar extraction surgery who accepted to participate in this research.

The inclusion criteria were: female, aged between 18 and 45 years, undergoing third molar removal at the Oral and Maxillofacial Surgery and Traumatology (OMS) service of UFPR, and agreeing to participate in the study. The exclusion criteria were pregnant women, breastfeeding, hormone replacement therapies, and menopause.

The sample size was calculated considering the following parameters: an estimated population of 400 women who undergo third molars extractions in 2 years at the University, an anticipated frequency of 50%, a confidence limit of 5%, and a design effect of 1. Using these parameters, the calculations resulted in a sample size of 197 women (www.openepi.com/samplesize) [30].

Genetic analysis

According to the previously described protocol [31], DNA was collected from mucosal cells using a mouthwash solution. The individual was instructed to rinse with 15 mL of saline solution for a period of 60 seconds. Afterward, the researcher gently scraped the buccal mucosa with a sterilized wooden spatula, and the samples were placed in Falcon tubes.

For DNA extraction, the samples were kept in a water bath after the addition of proteinase K (20mg/mL) for a period of 12 hours, followed by the addition of 10 mM ammonium acetate, 1 mM ethylenediamine tetraacetic acid (EDTA), 540 µL of isopropanol, 1000 µL of 70% ethanol, and finally, 50 µL of TE (TRIS 10mM; EDTA) with a predetermined centrifugation protocol [32]. The samples were stored in a freezer at -20°C.

Eleven polymorphisms from the genes *COMT*, *SLC6A4*, *TRPV1*, *HTR2A*, *ESR1* and *ESR2* were genotyped by the real-time polymerase chain reaction (PCR) technique using the StepOnePlusTM Real-Time PCR System (Thermo Fisher Scientific, Foster City, USA). All the polymorphisms used in this study were chosen if their minimum allele frequency was greater than 30%.

The polymorphisms *rs174675(T>C)* and *rs165656 (G>C)* in *COMT* were selected due to associated with alterations in anxiety levels in patients undergoing third molar extractions [7], disorders associated with persistent pain [33], schizophrenia [34], and chronic pain [35]. The polymorphism *rs3813034 (A>C)* in *SLC6A4* was chosen due to previous associations with pain and anxiety conditions [36,37]. The polymorphisms *rs8065080 (T>C)*, *rs222747 (C>T)* and *rs2224534 (A>G)* in *TRPV1* were used in this study because they are associated with acute pain sensitivity [38], delayed onset of anesthetic induction for dental extraction [39], neuropathic pain [40] and *rs4941573* (A>G) *rs6313* (G>A) in *HTR2A* due to previous investigations linking the polymorphisms to painful conditions [41,42] schizophrenia [43], neuropathic pain [44], mental health [45]. In relation to *rs2234693 (T>C)* in *ESR1* there are investigations on oral health-related quality of life [46] and depression [47]. The *rs4986938* (*C>T*) and *rs1256049* (*C>T*) polymorphisms in *ESR2* were included due to previous investigations on menstrual cycle-associated headache [48] and painful conditions [49]. Table 1 summarizes the genetic polymorphisms selected for the study.

Table 1. Characteristics of the genetic polymorphisms studied.

Gene	Polymorphisms	Locus	Change of Base	Minnor allele frequency/number of individuals assessed*
Catechol-O-methyltransferas (COMT)	*rs174675*	chr22(GRCh38.p14)	T/C	T=0.339537 C=0.67110
	rs165656		G/C	C=0.465310 G=0.4500
Solute Carrier Fami member 4 (SLC6A4)	*rs3813034*	chr17(GRCh38.p14)	A/C	A=0.17786 C=0.413042
Transient Receptor Potential Vanilloid Subfamily V Membe (TRPV1)	*rs8065080*	chr17:(GRCh38.p14)	T/C	T= 0.32193 C= 0.377096
	rs222747		C/G	C=0.225335 G=0.398
	rs224534		A/G	A=0.357086 G=0.2896
5-hydroxytryptamin receptor gene (HTR2A)	*rs4941573*	chr13:(GRCh38.p14)	G/A	A=0.45849 G=0.364725
	rs6113		G/A	G=0.48765 A=0.420112
Gene α do Receptor Estrogênio Humano (ESR1)	*rs2234693*	chr6:(GRCh38.p14)	C/T	T=0.497 C=0.462118
Gene β do Receptor Estrogênio Humano ESR2	*rs4986938*	chr14: (GRCh38.p14)	C/T	C=0.410 T=0.312044
	rs126049		C/T	C=0.458079 T=0.38

Source of information: https://www.ncbi.nlm.nih.gov/snp

Surgical Technique

All women participating in the study underwent the removal of third molars at the CTBMF service of UFPR. The surgical procedure was performed by residents in the first, second, or third year. For the anesthetic technique, 2% mepivacaine with 1:100,000 norepinephrine (Mepiadre®, DFL, Taquara, RJ, Brazil) was used. The surgical wound was closed with 4-0 nylon suture in all cases (Shalon medical®, Nova Suiça, Goiânia, Brazil). Surgical interventions were carried out in the afternoon (between 13:30 and 18:00), in an air-conditioned environment.

QCirDental questionnaire

QCirDental is a questionnaire developed and validated for the Brazilian Portuguese language to quantify the negative impact and discomfort associated with the surgical procedure. Immediately after the surgery,

participants completed the questionnaire in a separate room with the presence of the researcher only, who was previously trained to use the QCirDental questionnaire. The questionnaire consists of 20 items about the discomfort during the operative and the immediate postoperative periods answered on a scale from 0 (no discomfort) to 10 (highest level of discomfort). The degree of the effect (represented in this study as intensity of discomfort) is the sum of the scores of individual questions divided by the number of questions.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Science (IBM SPSS for Apple OS, version 25, IBM Corp. Armonk, USA). All inferential analyses considered a significance level of $p \leq 0.05$. The dependent variable was QCirDental scores, and the scores were compared between the categories of genetic variables. The QCirDental scores presented non-normal distribution according to the Kolmogorov-Smirnov test, and hence, the data were represented by median, minimum, and maximum. The difference between the QCirDental scores and the independent variables were analyzed using the Mann-Whitney U Test or the Kruskal-Wallis test (in more than two groups). Genotype distributions were evaluated in additive, dominant, and recessive models for the *COMT*, *SLC6A4*, *TRPV1*, *HTR2A* and *ESR2* genes. The Hardy-Weinberg equilibrium was evaluated by the Chi-square test.

RESULTS

Out of the total number of women approached to participate in the study, 35 were not included. In total, 207 participants were included. During the process, 7 women were excluded, all of whom did not undergo the surgical procedure due to systemic alterations that prevented surgery. Therefore, a sample of 200 women was obtained, totaling 416 extracted third molars. Only for the analysis of hormonal levels, 26 women were excluded. 19 due to the impossibility of blood collection and 7 because the reading of the exams was inconclusive (Figure 2). The median age of the sample was 24 years (ranging from 18 to 45). 97.5% of the participants in this study report discomfort on the 20 questions of the QCirDental instrument. The median score found for the instrument was 1.50 (ranging from 0 to 26).

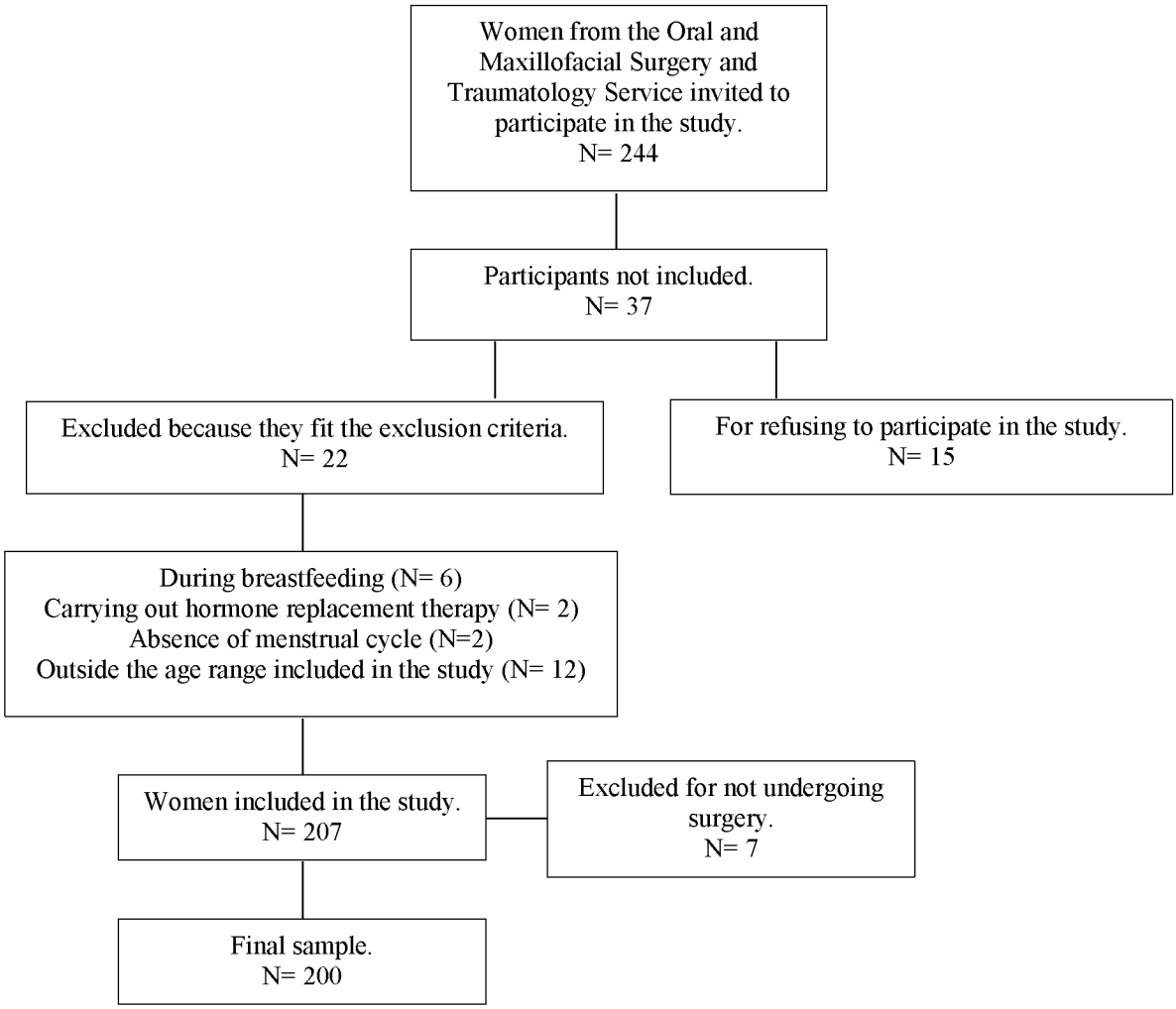

Figure 2. Flowchart illustrating the composition of the studied sample.

Table 2 shows the association between surgical discomfort and genetic polymorphisms in *COMT* and *SLC6A4*. For the genetic polymorphism *rs174675* in COMT, in the additive model, individual with TT genotype reported greater surgical discomfort with third molar surgery compared to individuals with CC ($p= 0.009$) and CT ($p= 0.008$) genotypes. In the dominant model, individuals with the TT genotype showed greater surgical discomfort than individuals with the CC/CT genotype ($p= 0.006$). No statistically significant differences were evident for the genetic polymorphisms *rs165656* and *rs3813034*.

Table 2. Association between the median (min and max) surgical discomfort with third molar extraction and gene polymorphisms *COMT* and *SLC6A4*.

Gene	Polymorphisms	Model			Surgical Discomfort Med (min – max)	*p-value*
COMT	*rs174675*	Additive	CC	N (95)	1.50 (0.1 – 26)[a]	***0.014****
			CT	N (25)	1.15 (0 – 3.8)[a]	
			TT	N (17)	2.80 (0.1 – 8.9)[b]	
		Dominant C	CC + CT	N (120)	1.45 (0 – 26)	***0.006***
			TT	N (17)	2.80 (0.1 – 8.9)	
		Recessive C	TT + CT	N (42)	1.70 (0 – 8.9)	0.429
			CC	N (95)	1.50 (0.1 – 26)	
	rs165656	Additive	CC	N (39)	1.95 (0.1 – 26)	0.168
			GC	N (72)	1.40 (0 – 5.6)	
			GG	N (40)	1.62 (0 – 8.9)	
		Dominant C	CC + GC	N (111)	1.55 (0 – 26)	0.741
			GG	N (40)	1.62 (0 – 8.9)	
		Recessive C	GG + GC	N (112)	1.42 (0 – 8.9)	0.105
			CC	N (39)	1.95 (0.1 – 26)	
SLC6A4	*rs3813034*	Additive	AA	N (25)	1.40 (0.2 – 26)	*0.394*
			CC	N (18)	0.95 (0.1 – 3.7)	
			AC	N (32)	1.27 (0 – 5.0)	
		Dominant A	AA/AC	N (57)	1.40 (0 – 26)	*0.199*
			CC	N (18)	0.95 (0.1 – 3.7)	
		Recessive A	CC/AC	N (50)	1.07 (0 – 5)	*0.351*
			AA	N (25)	1.40 (0.2 – 26)	

Kruskal-Wallis Test for additive model, with Mann-Whitney U post-test. Mann-Whitney U test for dominant and recessive models, with significance level of 0.05. Bold values indicate statistical significance.

Tables 3, 4 and 5 shows the association between surgical discomfort and genetic polymorphisms in *TRPV1, HTR2A, ESR1* and *ESR2*. No statistically significant differences were evident for the genetic polymorphisms *rs8065080, rs222747, rs2224534, rs491573, rs2234693, rs4986938* and *rs1256049 (p> 0.05)*. For the genetic polymorphism *rs6313* in *HTR2A*, in the dominant model, individual with GG genotype reported greater surgical discomfort with third molar surgery compared to individuals with AA/AG genotypes (*p= 0.038*).

Table 3. Association between the median (min and max) surgical discomfort with third molar extraction and gene polymorphisms *TRPV1*.

Gene	Polymorphisms	Model			Surgical Discomfort Med (min – max)	*p-value*
TRPV1	*rs8065080*	Additive	CC	N (18)	1.67 (0.2 – 5)	*0.761*
			CT	N (61)	1.50 (0 – 26)	
			TT	N (69)	1.50 (0 – 7.4)	
		Dominant C	CC + CT	N (79)	1.55 (0 – 26)	*0.845*
			TT	N (69)	1.50 (0 – 7.4)	
		Recessive C	TT + CT	N (130)	1.50 (0 – 26)	*0.461*
			CC	N (18)	1.67 (0.2 – 5)	
	rs222747	Additive	CC	N (4)	1.42 (1 – 2.6)	*0.327*
			CG	N (50)	1.52 (0 – 26)	
			GG	N (96)	1.42 (0 – 7.4)	
		Dominant C	CC + CG	N (77)	1.30 (0 – 7.4)	*0.157*
			GG	N (74)	1.67 (0 – 26)	
		Recessive C	GG + CG	N (147)	1.45 (0 – 26)	*0.803*
			CC	N (4)	1.42 (1.0 – 2.6)	
	rs2224534	Additive	AA	N (13)	1.70 (0 – 5)	*0.497*
			AG	N (62)	1.50 (0.1 – 14)	
			GG	N (73)	1.40 (0 – 7.4)	
		Dominant A	AA + AG	N (77)	1.55 (0 – 14)	*0.375*
			GG	N (73)	1.40 (0 – 7.4)	
		Recessive A	GG + AG	N (137)	1.50 (0 -14)	*0.311*
			AA	N (13)	1.70 (0 – 5.0)	

*Kruskal-Wallis Test for additive model and Mann-Whitney U test for dominant and recessive models, with significance level of 0.05.

Table 4. Association between the median (min and max) surgical discomfort with third molar extraction and gene polymorphisms *HTR2A*.

Gene	Polymorphisms	Model			Surgical Discomfort Med (min – max)	*p-value*
HTR2A	*rs4941573*	Additive	AA	N (70)	1.62 (0.1 – 26)	*0.364*
			AG	N (62)	1.55 (0 – 5.6)	
			GG	N (20)	1.05 (0.4 – 3.8)	
		Dominant A	AA + AG	N (132)	1.55 (0 – 26)	*0.340*
			GG	N (20)	1.05 (0.4 – 3.8)	
		Recessive A	GG + AG	N (82)	1.45 (0 – 5.6)	*0.184*
			AA	N (70)	1.62 (0.1 – 26)	
	rs6313	Additive	AA	N (7)	0.85 (0.1 – 2.7)	*0.107*
			AG	N (27)	1.30 (0.2 – 5.0)	
			GG	N (29)	1.80 (0.1 – 4.5)	
		Dominant A	AA + AG	N (83)	1.25 (0 – 5.7)	***0.038***
			GG	N (66)	1.75 (0.1 – 26)	
		Recessive A	GG + AG	N (128)	1.55 (0 – 26)	*0.269*
			AA	N (21)	0.9 (0 – 3.8)	

*Kruskal-Wallis Test for additive model and Mann-Whitney U test for dominant and recessive models, with significance level of 0.05. Bold values indicate statistical significance.

Table 5. Association between the median (min and max) surgical discomfort with third molar extraction and gene polymorphisms *ESR1* and *ESR2*.

Gene	Polymorphisms	Model			Surgical Discomfort Med (min – max)	*p-value*
ESR1	*rs2234693*	Additive	CC	N (11)	1.70 (0.2 – 3.8)	
			TT	N (23)	1.40 (0.1 – 5.6)	*0.692*
			CT	N (41)	1.80 (0 – 26)	
		Dominant C	CC + CT	N (52)	1.75 (0 – 26)	*0.428*
			TT	N (23)	1.40 (0.1 – 5.6)	
		Recessive C	TT + CT	N (64)	1.50 (0 – 26)	*0.922*
			CC	N (11)	1.70 (0.2 – 3.8)	
ESR2	*rs4986938*	Additive	CC	N (9)	2.25 (0.4 – 4.5)	
			CT	N (20)	1.45 (0 – 26)	*0.296*
			TT	N (36)	1.70 (0 – 14)	
		Dominant C	CC + CT	N (72)	1.70 (0 – 26)	*0.797*
			TT	N (8)	1.92 (0 – 4.5)	
		Recessive C	TT + CT	N (47)	1.80 (0 – 26)	*0.121*
			CC	N (33)	1.40 (0 – 5.0)	
	rs1256049	Additive	CC	N (62)	1.42 (0 – 26)	
			CT	N (3)	2 (1.9 – 4.9)	*0.203*
			TT	N (10)	2.07 (0 – 4.4)	
		Dominant C	CC + CT	N (86)	1.70 (0 – 26)	*0.617*
			TT	N (4)	2.07 (0.5 – 3.3)	
		Recessive C	TT + CT	N (13)	2.15 (0 – 4.9)	*0.084*
			CC	N (77)	1.50 (0 – 26)	

*Kruskal-Wallis Test for additive model and Mann-Whitney U test for dominant and recessive models, with significance level of 0.05.

DISCUSSION

Surgical procedures for the extraction of third molars are associated with the perception of discomfort [8]. This is a routine procedure in dental practice that requires professional attention, both in technique and scientific knowledge [7]. There is evidence that genetic polymorphisms are capable of influencing the perception of discomfort in individuals undergoing third molar removal [8].With the aim of improving patient-centered care, this study investigated whether genetic polymorphisms in *COMT*, *SLC6A4*, *TRPV1*, *HTR2A*, *ESR1*, and *ESR2* modulate the response of perception of surgical discomfort.

Regarding the influence of genetic polymorphisms, COMT plays an important role in the prefrontal cortex to coordinate and organize information from other parts of the brain. This region is related to personality, behavioral inhibition, and emotions. Polymorphisms in this gene can directly affect the stability and activity of catechol-O-methyltransferase, leading to inefficient information processing in the prefrontal cortex, thus playing an important role in determining the risks of diseases such as anxiety [50] and schizophrenia [51]. In our study, we found an association with the rs174675 polymorphism in COMT, where women with the TT genotype had significantly higher discomfort scores during surgery for the removal of third molars than those with the CC/CT genotype. A previous study associated the same polymorphism with depressive symptoms in Brazilian adolescents [52], and the same polymorphism has been linked to alterations in anxiety levels and vital signs in individuals undergoing third molar extractions [7].

Our study also found an association with the *rs6313* polymorphism in *HTR2A*, in the dominant model, genotype GG, and higher scores of discomfort perception during dental removal. The HTR2A gene encodes one of the serotonin receptors, a neurotransmitter with many functions. Mutations in this gene are associated with

susceptibility to schizophrenia [53] and stressful life events and suicide [54]. Changes in the serotonergic system can cause alterations in circuits linked to the amygdala, which is crucial in physiological-emotional modulation and response to aversive stimuli [54]. A previous study associated the *rs6313* variant with greater continuous pain and signs of central sensitization in patients with neuropathic pain [44].

Our findings contribute to the literature by supporting the effort to map genetic factors associated with patients experiencing more discomfort during dental treatment. A previous study indicated an association between individuals with the AA genotype and the rs3800373 polymorphism of the FKBP5 gene, and a heightened perception of discomfort during the removal of third molars [8]. Individualization is of particular importance in managing conditions related to sensitivity, perception, and pain due to the high individual variability found in these characteristics [55–57].

Regarding the limitations of this study, our sample may not be representative, and we did not evaluate the entire genes, but only part of them. Although we did not find significant associations between polymorphisms in the *SLC6A4*, *TRPV1*, *ESR1*, and *ESR2* genes, we encourage the development of further studies on discomfort perception during dental extractions associated with these polymorphisms. Our results indicate that the *rs174675* polymorphism in *COMT* for women with the TT genotype and the *rs6313* polymorphism in *HTR2A* for the GG genotype are associated with a greater perception of discomfort during the removal of third molars.

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6. CONCLUSÕES

Mulheres com IMC elevado, fase folicular do ciclo menstrual, não ter filhos, menor número de filhos, maior duração do procedimento cirúrgico, altos escores do traço de ansiedade, experiência traumática em cirurgia odontológica, uso de medicamentos para ansiedade e depressão, genótipo TT para o *rs174675* do gene *COMT,* genótipo GG para o *rs6113* do gene *HTR2A*, foram variáveis associadas à maior percepção de desconforto durante a extração dentária.

Nossos achados reforçam que diversos fatores estão associados à percepção de desconforto, sugerindo a adoção de um modelo individualizado para controle da dor e do desconforto.

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ANEXO 1 - PARECER CONSUBSTANCIADO DO CEP

UFPR - SETOR DE CIÊNCIAS DA SAÚDE DA UNIVERSIDADE FEDERAL DO PARANÁ - SCS/UFPR

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: EFEITO DAS DIFERENTES FASES DO CICLO MENSTRUAL SOBRE A PERCEPÇÃO DE DESCONFORTO CIRÚRGICO NA REMOÇÃO DE TERCEIROS

Pesquisador: RAFAELA SCARIOT

Área Temática: Genética Humana:
(Trata-se de pesquisa envolvendo Genética Humana que não necessita de análise ética por parte da CONEP;);

Versão: 4

CAAE: 43894621.3.0000.0102

Instituição Proponente: Departamento de Estomatologia

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 5.731.919

Apresentação do Projeto:

O projeto de pesquisa e da prof. Dr. Rafaela Scariot (departamento de Estomatolgia) com colaboracao do prof. Dr. Nelson Luis Barbosa Rebellato (departamento de Estomatologia) e da doutoranda Gisele Emilaine da Silva Reis. E uma pesquisa que envolve genetica humana, mas segundo os pesquisadores nao necessita de analise etica pela CONEP. E um estudo transversal observacional, que pretende incluir 260 participantes.

O periodo inicialmente proposto para a realizacao da pesquisa e apos a aprovacao do CEP ate julho de 2023, sendo que o delineamento da pesquisa e elaboracao do projeto foi inicado em 2020.

O recrutamento das participantes ocorrera na sala de espera do centro cirurgico de Cirurgia e Traumatologia Bucomaxilofaciais (CTBMF) da Universidade Federal do Parana (UFPR), antes da paciente passar pela etapa do exame clinico previo ao procedimento cirurgico. A pesquisa pretende correlacionar as diferentes fases do ciclo menstrual e polimorfismos geneticos com a precepcao de dor e desconforto em cirugias para extracao de tereiros molares.

Na presente emenda, a pesquisadora principal solicita as seguintes alteracoes:

1. Alteracao no metodo de coleta e analise de fluido corporal para verificacao dos niveis hormonais
2. Adicao de um hormonio a ser analisado

Endereço: Rua Padre Camargo, 285 - 1° andar
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3. Adicao de tres perguntas na ficha de anamnese (Anexo I) 4. Reducao no numero amostral
5. Alteracao cronograma

Itens a serem contemplados:
- O fluido a ser coletado deixara de ser a saliva e passara a ser o sangue.
- Adicionar a analise do hormonio Hormonio Foliculo Estimulante (FSH).
- Adicionar a ficha de anamnese (Anexo I) as seguintes perguntas:
- De 0 a 10 quanto doeu a coleta de sangue?
- Voce possui algum tipo de dor cronica no corpo ou no rosto?
- Voce toma algum medicamento?
- O numero amostral foi reduzido devido a um atraso para inicio do projeto, em consequencia da pandemia. - Foram adicionados 3 meses para a etapa de coleta de dados, que antes finalizaria em 03/2023 e passara a se encerrar em 08/2023.

A seguinte justificativa para a emenda foi apresentada:

Justificativa da emenda

"Para a analise hormonal de estrogenio e progesterona atraves da saliva e necessario que a participante esteja sem se alimentar ou ingerir bebidas pelo tempo de 60 minutos antes da coleta de saliva, isso inviabilizou esse metodo pois, as cirurgias para remocao de terceiros molares sempre ocorrem no periodo da tarde, as 13:30h, sendo as pacientes aconselhadas a se alimentarem antes de passar pelo procedimento cirurgico, pois isso confere maior seguranca a saude e bem estar da paciente que passara pela remocao dentaria. Alem disso, e importante que o hormonio Foliculo Estimulante seja analisado para que haja uma melhor exatidao da fase do ciclo menstrual e para isso, e necessario analise do fluido sanguineo ou urinario (Schmalenberger, 2021). Ademais, ocorre uma controversia em relacao a concordancia entre os niveis sericos do estrogenio atraves de coletas por amostras de saliva e sangue (Choe JK, 1983; Schmalenberger, 2021). E importante salientar que a pesquisadora responsavel possui habilitacao em coleta sanguinea, estando apta para realizar este procedimento.
Com a alteracao do metodo de coleta do fluido corporal, achamos que seria interessante adicionar a seguinte pergunta: "De 0 a 10 quanto doeu a coleta de sangue?", assim teremos uma compreensao a mais em relacao a percepcao de dor/desconforto de acordo com as diferentes

fases do ciclo menstrual. A adicao das perguntas "Voce possui algum tipo de dor cronica no corpo ou no rosto?" e "Voce toma algum medicamento?" nos parecem importante pois podem influenciar na resposta a dor/desconforto que paciente ira sentir durante a remocao do terceiro molar.
Alem disso, foi necessario alterar o cronograma devido a pandemia e com isso, houve reducao no tempo total de coleta de dados e, por consequencia uma reducao no tamanho amostral."

Objetivo da Pesquisa:
Os objetivos da versao inicial do projeto foram os seguintes:

Objetivo Geral

Investigar o efeito das diferentes fases do ciclo menstrual na intensidade de percepcao de desconforto cirurgico durante a remocao de terceiros molares.

Objetivos Especificos

Avaliar a influencia dos fatores biopsicossociais na intensidade de percepcao de desconforto cirurgico durante a remocao de terceiros molares;
Investigar o efeito das caracteristicas cirurgicas, anatomicas e radiograficas na intensidade de percepcao de desconforto cirurgico durante a remocao de terceiros molares;
Verificar se a presenca de disfuncao temporomandibular esta associada a intensidade de percepcao de desconforto cirurgico durante a remocao de terceiros molares;
Investigar associacao de polimorfismos nos genes COMT, FKBP5, ESR1, ESR2 e PROGINS com a intensidade de percepcao de desconforto cirurgico durante a remocao de terceiros molares."

Avaliação dos Riscos e Benefícios:
Os riscos e beneficios previstos na versao inicial do projeto foram os seguintes:

"Quais os beneficios, diretos ou indiretos, para a populacao e a sociedade?
A investigacao dos fatores que contribuem para as diferencas individuais na dor pode fornecer informacoes essenciais para a aquisicao de padroes, o que pode levar ao desenvolvimento de novos tratamentos personalizados. Alem disso, os resultados desse estudo permitirao a aquisicao de dados iniciais para o entendimento da influencia do periodo do ciclo menstrual na percepcao de

desconforto durante a remocao de terceiros molares, permitindo uma padronizacao no no servico de CTBMF da UFPR.

Quais os riscos inerentes ou decorrentes da pesquisa? O paciente pode apresentar um pequeno desconforto tambem ao ser realizada raspagem da mucosa jugal constrangimento do paciente (devido a perguntas necessarias, contudo, para a pesquisa se tornam
periodo ideal para agendamento de cirurgias eletivas no momento da realizacao do exame do DC/TMD e para coleta de DNA. Outra possivel ocorrencia e o pessoais que muitas vezes para ele nao sejam importantes).

Qual a possibilidade da ocorrencia?
Minima, pois em todas as etapas os pesquisadores responsaveis pela coleta dos dados estarao atentos e prestando os devidos cuidados para nao ocasionar nenhum incomodo ou constrangimento ao participante da pesquisa. Vale ressaltar que sera esclarecido ao participante que ele podera desistir da pesquisa em qualquer momento, sem nenhum onus, caso sinta algum desconforto durante o exame ou ao responder as perguntas.

Quais as medidas para minimizacao e protecao do participante da pesquisa?
A pesquisa ficara restrita somente aos pesquisadores aqui citados, ficando sobre responsabilidade dos mesmos esclarecer todas as duvidas das participantes bem como explicar a importancia de cada passo presente no estudo, desde o preenchimento da ficha de informacoes individuais de cada um a coleta biologica do DNA. Ainda, a fim de evitar possiveis problemas mencionados anteriormente, havera um cuidado redobrado na busca de um lugar que vise conforto a participante, para que assim ela possa sentir-se bem durante os poucos minutos que participara do estudo. Para a coleta de saliva e celulas da mucosa jugal da paciente, uma alternativa para minimizar o desconforto ao realizar a raspagem da mucosa com espatula de madeira, e realizar o procedimento em local reservado, estando presente somente o pesquisador e o participante. Outra possibilidade e realizar movimento unico de raspagem da mucosa e alertar a participante que em caso de desconforto o procedimento sera interrompido ate que ela se sinta confortavel para realizar novamente. Caso o desconforto seja demais a participante, a mesmo pode optar por nao o realizar. Vale ressaltar que as participantes diagnosticadas com desordens temporomandibulares serao encaminhadas para receber tratamento na clinica de DTM e Dor Orofacial da UFPR."

Comentários e Considerações sobre a Pesquisa:

Trata-se de uma pesquisa muito bem fundamentada para investigar a percepcao de dor de mulheres durante a extracao dos terceiros molares, em dferentes fases do ciclo menstrual.

Alem das ferramentas para mensurar dor e desconforto, os pesquisadores irao fazer analise genetica por meio da coleta de material da mucosa jugal.

Considerações sobre os Termos de apresentação obrigatória:

Os termos foram apresentados.

Recomendações:

Não há.

Conclusões ou Pendências e Lista de Inadequações:

A emenda esta bem fundamentada e as inclusoes propostas estao condizentes com o projeto.

A pendência apontada em parecer anterior foi corrigida.

Considerações Finais a critério do CEP:

Solicitamos que sejam apresentados a este CEP, relatórios semestrais e final, a cada seis meses da primeira aprovação de seu protocolo, sobre o andamento da pesquisa, bem como informações relativas às modificações do protocolo, cancelamento, encerramento e destino dos conhecimentos obtidos, através da Plataforma Brasil - no modo: NOTIFICAÇÃO. Demais alterações e prorrogação de prazo devem ser enviadas no modo EMENDA. Lembrando que o cronograma de execução da pesquisa deve ser atualizado no sistema Plataforma Brasil antes de enviar solicitação de prorrogação de prazo. Emenda – ver modelo de carta em nossa página: www.cometica.ufpr.br (obrigatório envio)

- Favor inserir em seu TCLE e TALE o número do CAAE e o número deste Parecer de aprovação, para que possa aplicar aos participantes de sua pesquisa, conforme decisão da Coordenação do CEP/SD de 13 de julho de 2020.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1994492_E1.pdf	29/09/2022 20:36:51		Aceito
Outros	Carta_resposta_pendencias.docx	29/09/2022 20:36:26	RAFAELA SCARIOT	Aceito
Outros	concordancia_servicos_envolvidos_pendencia.pdf	29/09/2022 20:35:31	RAFAELA SCARIOT	Aceito
Brochura Pesquisa	Projeto_detalhado_pendencia.docx	29/09/2022 20:35:16	RAFAELA SCARIOT	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_detalhado_emenda.docx	04/08/2022 22:53:11	RAFAELA SCARIOT	Aceito
Outros	emenda.docx	04/08/2022 22:51:08	RAFAELA SCARIOT	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_emenda.docx	04/08/2022 22:50:27	RAFAELA SCARIOT	Aceito
Outros	carta_resposta_parecerista.docx	04/04/2021 12:20:55	RAFAELA SCARIOT	Aceito
Outros	analise_de_merito.pdf	02/03/2021 10:58:03	Rafaela Scariot	Aceito
Folha de Rosto	Folha_de_rosto.pdf	01/03/2021 16:35:01	Rafaela Scariot	Aceito
Outros	Check_List.pdf	24/02/2021 11:12:13	Rafaela Scariot	Aceito
Outros	termo_guarda_material_biologico.pdf	24/02/2021 11:09:13	Rafaela Scariot	Aceito
Declaração de Pesquisadores	declaracao_compromisso.pdf	24/02/2021 11:06:27	Rafaela Scariot	Aceito
Outros	concordancia_servicos_envolvidos_2.pdf	24/02/2021 11:05:53	Rafaela Scariot	Aceito
Declaração de concordância	concordancia_dos_servicos_envolvidos.pdf	24/02/2021 10:58:58	Rafaela Scariot	Aceito
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Outros	carta_encaminhamento_pesquisador_cep.pdf	24/02/2021 10:45:47	Rafaela Scariot	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

CURITIBA, 31 de Outubro de 2022

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ANEXO 2 – INSTRUMENTO IDATE

Escala de Ansiedade-Traço

Número:

Leia cada pergunta e faça um X na alternativa que melhor indicar como você geralmente se sente.
Não gaste muito tempo numa única afirmação, mas tente dar a resposta que mais se aproximar de como você se sente geralmente:

		Quase nunca	Às vezes	Frequentemente	Quase Sempre
1.	Sinto-me bem				
2.	Canso-me facilmente				
3.	Tenho vontade de chorar				
4.	Gostaria de poder ser tão feliz quanto os outros parecem				
5.	Perco oportunidades porque não consigo tomar decisões rapidamente				
6.	Sinto-me descansado				
7.	Sou calmo, ponderado e senhor de mim mesmo				
8.	Sinto que as dificuldades estão se acumulando de tal forma que não consigo resolver				
9.	Preocupo-me demais com as coisas sem importância				
10.	Sou feliz				
11.	Deixo-me afetar muito pelas coisas				
12.	Não tenho muita confiança em mim mesmo				
13.	Sinto-me seguro				
14.	Evito ter que enfrentar crises ou problemas				
15.	Sinto-me deprimido				
16.	Estou satisfeito				
17.	Idéias sem importância me entram na cabeça e ficam me preocupando				
18.	Levo os desapontamentos tão a sério que não consigo tirá-los da cabeça				
19.	Sou uma pessoa estável				
20.	Fico tenso e perturbado quando penso em meus problemas do momento				
	TOTAL somatória das alternativas assinaladas				

Escala de Ansiedade- Estado

Leia cada pergunta e faça um círculo ao redor do número à direita da afirmação que melhor indicar como você se sente agora, neste momento.Não gaste muito tempo numa única afirmação, mas tente dar uma resposta que mais se aproxime de como você se sente neste momento.

		Muitíssimo	Bastante	Um pouco	Absolutamente não
1.	Sinto-me calmo				
2.	Sinto-me seguro				
3.	Estou tenso				
4.	Estou arrependido				
5.	Sinto-me à vontade				
6.	Sinto-me perturbado				
7.	Estou preocupado com possíveis infortúnios				
8.	Sinto-me descansado				
9.	Sinto-me ansioso				
10.	Sinto-me "em casa"				
11.	Sinto-me confiante				
12.	Sinto-me nervoso				
13.	Estou agitado				
14.	Sinto-me uma pilha de nervos				
15.	Estou descontraído				
16.	Sinto-me satisfeito				
17.	Estou preocupado				
18.	Sinto-me confuso				
19.	Sinto-me alegre				
20.	Sinto-me bem				
	TOTAL somatória das alternativas assinaladas				

ANEXO 3 – INSTRUMENTO QCirDental

Questionário QCirDental

Número:

QUESTIONÁRIO DE AUTO-PERCEPÇÃO DE CIRURGIA BUCAL DENTO-ALVEOLAR (QCirDental)

Tente classificar o que mais lhe INCOMODOU durante a cirurgia em sua boca, conforme apergunta.

USE A ESCALA, e selecione um número que melhor corresponde como você se sentiu.

0	1	2	3	4	5	6	7	8	9	10
Não incomodou nada ou a pergunta não se aplica para minha cirurgia										Incomodou demais ou muito/ um absurdo

		Nota
1. Eu me senti nervoso durante a cirurgia		1.
2. Os comentários que os cirurgiões ou auxiliares fizeram durante a minha cirurgia		2.
3. Os líquidos e sangue na minha boca		3.
4. A impressão que eu tive dos machucados na minha boca		4.
5. Eu tive medo da anestesia		5.
6. A dor que eu senti durante a anestesia		6.
7. A dor que eu senti durante a cirurgia		7.
8. Os barulhos dos instrumentos		8.
9. O tempo que a cirurgia levou		9.
10. A falta de explicação do que estava acontecendo durante a cirurgia	E isso me	10.
11. A falta de delicadeza ou cuidado do cirurgião para comigo durante a cirurgia	incomodou	11.
12. Eu me senti indignado durante a cirurgia (por qualquer motivo relacionado)		12.
13. A dificuldade do cirurgião para terminar a cirurgia		13.
14. Durante a minha cirurgia, senti a minha privacidade invadida		14.
15. O lugar, o ambiente		15.
16. Os cheiros diferentes		16.
17. Os materiais ou instrumentos que colocaram na minha boca		17.
18. Eu me senti angustiado durante a cirurgia		18.
19. A falta de explicações após terminar a cirurgia		19.
20. A sensação de ter perdido meu(s) dente(s)		20.

Você faria algum outro comentário:

ANEXO 4 – NORMAS DA REVISTA

Clinical Oral Investigations

2023 Impact factor: 3.4

ISSN: 1436-3771

Classificação de periódicos (Qualis): A1

Instructions for Authors

Types of papers

Papers may be submitted for the following sections:

Research Article

Reviews

Brief Report – with up to 2000 words and up to two figures and/or tables

Correspondence (Discussion paper)

Debate (Letter to the Editor)

Perspective (by Editor invitation only)

Perspective articles are focused articles on topics of interest to a broad audience, but are written from a personal viewpoint. They are intended to provide a forum to be more speculative than Reviews, but should remain balanced and are intended to cover timely and relevant topics. These articles are peer reviewed.

Limited to 1,500-3,000 words (excluding abstract, references and figure legends); Unstructured abstract 200 words; 4 tables/figures; 60 references

It is the general policy of this journal not to accept case reports and pilot studies.

Editorial Procedure

Clinical Oral Investigations operates a single-blind peer-review system, where the reviewers are aware of the names and affiliations of the authors, but the reviewer reports provided to authors are anonymous.

Submitted manuscripts will generally be reviewed by two or more experts who will be asked to evaluate whether the manuscript is scientifically sound and coherent, whether it duplicates already published work, and whether or not the manuscript is sufficiently clear for publication. The Editors will reach a decision based on these reports and, where necessary, they will consult with members of the Editorial Board.

Summary of the editorial process

The author submits a manuscript and the Editorial Office performs an initial quality check on the manuscript to ensure that the paper is formatted correctly

The manuscript receives a tracking number and Manuscripts are assigned to an Editor-in-Chief or a Section Editor for an initial editorial assessment. If the decision is not to send the manuscript for review, the Editor contacts the author with the decision.

If the Editor decides the paper is within the Journal's remit, peer reviewers are selected and assigned. This can take some time dependent on the responsiveness and availability of the reviewers selected.

Reviewers are given 14 days from acceptance to submit their reports. Once the required reports are submitted, the Associate Editor will give a recommendation or the Editor-in-Chief makes a final decision based on the comments received. The final decision is the sole responsibility of the Editors-in-Chief.

Manuscript Submission

Submission of a manuscript implies: that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities – tacitly or explicitly – at the institute where the work has been carried out. The publisher will not be held legally responsible should there be any claims for compensation.

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Authors wishing to include figures, tables, or text passages that have already been published elsewhere are required to obtain permission from the copyright owner(s) for both the print and online format and to include evidence that such permission has been granted when submitting their papers. Any material received without such evidence will be assumed to originate from the authors.

Online Submission

Please follow the hyperlink “Submit manuscript” and upload all of your manuscript files following the instructions given on the screen.

Source Files

Please ensure you provide all relevant editable source files at every submission and revision. Failing to submit a complete set of editable source files will result in your article not being considered for review. For your manuscript text please always submit in common word processing formats such as .docx or LaTeX.

Springer Author Academy

The Springer Author Academy is a set of comprehensive online training pages mainly geared towards first-time authors. At this point, more than 50 pages offer advice to authors on how to write and publish a journal article.

Title Page

The title page should include:

The name(s) of the author(s)

A concise and informative title

The affiliation(s) and address(es) of the author(s)

The e-mail address, telephone and fax numbers of the corresponding author

Abstract

Please provide a structured abstract of 150 to 250 words which should be divided into the following sections:

Objectives (stating the main purposes and research question)

Materials and Methods

Results

Conclusions

Clinical Relevance

These headings must appear in the abstract.

Keywords

Please provide 4 to 6 keywords which can be used for indexing purposes.

Text Formatting

Manuscripts should be submitted in Word.

Use a normal, plain font (e.g., 10-point Times Roman) for text.

Use italics for emphasis.

Use the automatic page numbering function to number the pages.

Do not use field functions.

Use tab stops or other commands for indents, not the space bar.

Use the table function, not spreadsheets, to make tables.

Use the equation editor or MathType for equations.

Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Manuscripts with mathematical content can also be submitted in LaTeX. We recommend using Springer Nature's LaTeX template.

Headings

Please use no more than three levels of displayed headings.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and

other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

References

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].

2. This result was later contradicted by Becker and Seligman [5].

3. This effect has been widely studied [1-3, 7].

Reference list

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text.

The entries in the list should be numbered consecutively.

If available, please always include DOIs as full DOI links in your reference list (e.g. “https://doi.org/abc”).

Journal article

Gamelin FX, Baquet G, Berthoin S, Thevenet D, Nourry C, Nottin S, Bosquet L (2009) Effect of high intensity intermittent training on heart rate variability in prepubescent children. Eur J Appl Physiol 105:731-738. https://doi.org/10.1007/s00421-008-0955-8

Ideally, the names of all authors should be provided, but the usage of “et al” in long author lists will also be accepted:

Smith J, Jones M Jr, Houghton L et al (1999) Future of health insurance. N Engl J Med 965:325–329

Article by DOI

Slifka MK, Whitton JL (2000) Clinical implications of dysregulated cytokine production. J Mol Med. https://doi.org/10.1007/s001090000086

Book

South J, Blass B (2001) The future of modern genomics. Blackwell, London

Book chapter

Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) The rise of modern genomics, 3rd edn. Wiley, New York, pp 230-257

Online document

Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. http://physicsweb.org/articles/news/11/6/16/1. Accessed 26 June 2007

Dissertation

Trent JW (1975) Experimental acute renal failure. Dissertation, University of California

Always use the standard abbreviation of a journal's name according to the ISSN List of Title Word Abbreviations, see

ISSN.org LTWA

If you are unsure, please use the full journal title.

Authors preparing their manuscript in LaTeX can use the bibliography style file sn-basic.bst which is included in the Springer Nature Article Template.

Tables

All tables are to be numbered using Arabic numerals.

Tables should always be cited in text in consecutive numerical order.

For each table, please supply a table caption (title) explaining the components of the table.

Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.

Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

Artwork and Illustrations Guidelines

Electronic Figure Submission

Supply all figures electronically.

Indicate what graphics program was used to create the artwork.

For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MSOffice files are also acceptable.

Vector graphics containing fonts must have the fonts embedded in the files.

Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

Definition: Black and white graphic with no shading.

Do not use faint lines and/or lettering and check that all lines and lettering within the figures are legible at final size.

All lines should be at least 0.1 mm (0.3 pt) wide.

Scanned line drawings and line drawings in bitmap format should have a minimum resolution of 1200 dpi.

Vector graphics containing fonts must have the fonts embedded in the files.

Halftone Art

Definition: Photographs, drawings, or paintings with fine shading, etc.

If any magnification is used in the photographs, indicate this by using scale bars within the figures themselves.

Halftones should have a minimum resolution of 300 dpi.

Combination Art

Definition: a combination of halftone and line art, e.g., halftones containing line drawing, extensive lettering, color diagrams, etc.

Combination artwork should have a minimum resolution of 600 dpi.

Color Art

Color art is free of charge for online publication.

If black and white will be shown in the print version, make sure that the main information will still be visible. Many colors are not distinguishable from one another when converted to black and white. A simple way to check this is to make a xerographic copy to see if the necessary distinctions between the different colors are still apparent.

If the figures will be printed in black and white, do not refer to color in the captions.

Color illustrations should be submitted as RGB (8 bits per channel).

Figure Lettering

To add lettering, it is best to use Helvetica or Arial (sans serif fonts).

Keep lettering consistently sized throughout your final-sized artwork, usually about 2–3 mm (8–12 pt).

Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label.

Avoid effects such as shading, outline letters, etc.

Do not include titles or captions within your illustrations.

Figure Numbering

All figures are to be numbered using Arabic numerals.

Figures should always be cited in text in consecutive numerical order.

Figure parts should be denoted by lowercase letters (a, b, c, etc.).

If an appendix appears in your article and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix

figures,"A1, A2, A3, etc." Figures in online appendices [Supplementary Information (SI)] should, however, be numbered separately.

Figure Captions

Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file.

Figure captions begin with the term Fig. in bold type, followed by the figure number, also in bold type.

No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption.

Identify all elements found in the figure in the figure caption; and use boxes, circles, etc., as coordinate points in graphs.

Identify previously published material by giving the original source in the form of a reference citation at the end of the figure caption.

Figure Placement and Size

Figures should be submitted within the body of the text. Only if the file size of the manuscript causes problems in uploading it, the large figures should be submitted separately from the text.

When preparing your figures, size figures to fit in the column width.

For large-sized journals the figures should be 84 mm (for double-column text areas), or 174 mm (for single-column text areas) wide and not higher than 234 mm.

For small-sized journals, the figures should be 119 mm wide and not higher than 195 mm.

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If you include figures that have already been published elsewhere, you must obtain permission from the copyright owner(s) for both the print and online format. Please be aware that some publishers do not grant electronic rights for free and that Springer will not be able to refund any costs that may have occurred to receive these permissions. In such cases, material from other sources should be used.

Accessibility

In order to give people of all abilities and disabilities access to the content of your figures, please make sure that

All figures have descriptive captions (blind users could then use a text-to-speech software or a text-to-Braille hardware)

Patterns are used instead of or in addition to colors for conveying information (colorblind users would then be able to distinguish the visual elements)

Any figure lettering has a contrast ratio of at least 4.5:1

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Supplementary Information (SI)

Springer accepts electronic multimedia files (animations, movies, audio, etc.) and other supplementary files to be published online along with an article or a book chapter. This feature can add dimension to the author's article, as certain information cannot be printed or is more convenient in electronic form.

Before submitting research datasets as Supplementary Information, authors should read the journal's Research data policy. We encourage research data to be archived in data repositories wherever possible.

Submission

Supply all supplementary material in standard file formats.

Please include in each file the following information: article title, journal name, author names; affiliation and e-mail address of the corresponding author.

To accommodate user downloads, please keep in mind that larger-sized files may require very long download times and that some users may experience other problems during downloading.

High resolution (streamable quality) videos can be submitted up to a maximum of 25GB; low resolution videos should not be larger than 5GB.

Audio, Video, and Animations

Aspect ratio: 16:9 or 4:3

Maximum file size: 25 GB for high resolution files; 5 GB for low resolution files

Minimum video duration: 1 sec

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Text and Presentations

Submit your material in PDF format; .doc or .ppt files are not suitable for long-term viability.

A collection of figures may also be combined in a PDF file.

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Spreadsheets should be submitted as .csv or .xlsx files (MS Excel).

Specialized Formats

Specialized format such as .pdb (chemical), .wrl (VRML), .nb (Mathematica notebook), and .tex can also be supplied.

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It is possible to collect multiple files in a .zip or .gz file.

Numbering

If supplying any supplementary material, the text must make specific mention of the material as a citation, similar to that of figures and tables.

Refer to the supplementary files as “Online Resource”, e.g., "... as shown in the animation (Online Resource 3)", “... additional data are given in Online Resource 4”.

Name the files consecutively, e.g. “ESM_3.mpg”, “ESM_4.pdf”.

Captions

For each supplementary material, please supply a concise caption describing the content of the file.

Processing of supplementary files

Supplementary Information (SI) will be published as received from the author without any conversion, editing, or reformatting.

Accessibility

In order to give people of all abilities and disabilities access to the content of your supplementary files, please make sure that

The manuscript contains a descriptive caption for each supplementary material

Video files do not contain anything that flashes more than three times per second (so that users prone to seizures caused by such effects are not put at risk)

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Clinical Trial Registration

Clinical trials must be registered prior to submission of manuscripts. The registration site must be publicly available in English.

Recommended sites are: https://www.isrctn.com ; https://www.clinicaltrialsregister.eu; https://clinicaltrials.gov or similar.

The registration number is required for the submission and must appear on the title page.

Editing Services

English

How can you help improve your manuscript for publication?

Presenting your work in a well-structured manuscript and in well-written English gives it its best chance for editors and reviewers to understand it and evaluate it fairly. Many researchers find that getting some independent support helps them present their results in the best possible light. The experts at Springer Nature Author Services can help you with manuscript preparation—including English language editing, developmental comments, manuscript formatting, figure preparation, translation, and more.

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This journal is committed to upholding the integrity of the scientific record. As a member of the Committee on Publication Ethics (COPE) the journal will follow the COPE guidelines on how to deal with potential acts of misconduct.

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The submitted work should be original and should not have been published elsewhere in any form or language (partially or in full), unless the new work concerns an expansion of previous work. (Please provide transparency on the re-use of material to avoid the concerns about text-recycling ('self-plagiarism').

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Authors should make sure they have permissions for the use of software, questionnaires/(web) surveys and scales in their studies (if appropriate).

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Research that may be misapplied to pose a threat to public health or national security should be clearly identified in the manuscript (e.g. dual use of research). Examples include creation of harmful consequences of biological agents or toxins, disruption of immunity of vaccines, unusual hazards in the use of chemicals, weaponization of research/technology (amongst others).

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*All of the above are guidelines and authors need to make sure to respect third parties rights such as copyright and/or moral rights.

Upon request authors should be prepared to send relevant documentation or data in order to verify the validity of the results presented. This could be in the form of raw data, samples, records, etc. Sensitive information in the form of confidential or proprietary data is excluded.

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- an expression of concern may be placed with the article

- or in severe cases retraction of the article may occur.

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The author's institution may be informed

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Authors have an obligation to correct mistakes once they discover a significant error or inaccuracy in their published article. The author(s) is/are requested to contact the journal and explain in what sense the error is impacting the article. A decision on how to correct the literature will depend on the nature of the error. This may be a correction or retraction. The retraction note should provide transparency which parts of the article are impacted by the error.

Suggesting / excluding reviewers

Authors are welcome to suggest suitable reviewers and/or request the exclusion of certain individuals when they submit their manuscripts. When suggesting reviewers, authors should make sure they are totally independent and not connected to the work in any way. It is strongly recommended to suggest a mix of reviewers from different countries and different institutions. When suggesting reviewers, the Corresponding Author must provide an institutional email address for each suggested reviewer, or, if this is not possible to include other means of verifying the identity such as a link to a personal homepage, a link to the publication record or a researcher or author ID in the submission letter. Please note that the Journal may not use the suggestions, but suggestions are appreciated and may help facilitate the peer review process.

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These guidelines describe authorship principles and good authorship practices to which prospective authors should adhere to.

Authorship clarified

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The Publisher does not prescribe the kinds of contributions that warrant authorship. It is recommended that authors adhere to the guidelines for authorship that are applicable in their specific research field. In absence of specific guidelines it is recommended to adhere to the following guidelines*:

All authors whose names appear on the submission

1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work;

2) drafted the work or revised it critically for important intellectual content;

3) approved the version to be published; and

4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

* Based on/adapted from:

ICMJE, Defining the Role of Authors and Contributors,

Transparency in authors' contributions and responsibilities to promote integrity in scientific publication, McNutt at all, PNAS February 27, 2018

Disclosures and declarations

All authors are requested to include information regarding sources of funding, financial or non-financial interests, study-specific approval by the appropriate ethics committee for research involving humans and/or animals, informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals (as appropriate).

The decision whether such information should be included is not only dependent on the scope of the journal, but also the scope of the article. Work submitted for publication may have implications for public health or general welfare and in those cases it is the responsibility of all authors to include the appropriate disclosures and declarations.

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All authors are requested to make sure that all data and materials as well as software application or custom code support their published claims and comply with field standards. Please note that journals may have individual policies on (sharing) research data in concordance with disciplinary norms and expectations.

Role of the Corresponding Author

One author is assigned as Corresponding Author and acts on behalf of all co-authors and ensures that questions related to the accuracy or integrity of any part of the work are appropriately addressed.

The Corresponding Author is responsible for the following requirements:

ensuring that all listed authors have approved the manuscript before submission, including the names and order of authors;

managing all communication between the Journal and all co-authors, before and after publication;*

providing transparency on re-use of material and mention any unpublished material (for example manuscripts in press) included in the manuscript in a cover letter to the Editor;

making sure disclosures, declarations and transparency on data statements from all authors are included in the manuscript as appropriate (see above).

* The requirement of managing all communication between the journal and all co-authors during submission and proofing may be delegated to a Contact or Submitting Author. In this case please make sure the Corresponding Author is clearly indicated in the manuscript.

Author contributions

In absence of specific instructions and in research fields where it is possible to describe discrete efforts, the Publisher recommends authors to include contribution statements in the work that specifies the contribution of every author in order to promote transparency. These contributions should be listed at the separate title page.

Examples of such statement(s) are shown below:

Free text:

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [full name], [full name] and [full name]. The first draft of the manuscript was written by [full name] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Example: CRediT taxonomy:

· Conceptualization: [full name], …; Methodology: [full name], …; Formal analysis and investigation: [full name], …; Writing - original draft preparation: [full name, …]; Writing - review and editing: [full name], …; Funding acquisition: [full name], …; Resources: [full name], …; Supervision: [full name],….

For review articles where discrete statements are less applicable a statement should be included who had the idea for the article, who performed the literature search and data analysis, and who drafted and/or critically revised the work.

For articles that are based primarily on the student's dissertation or thesis, it is recommended that the student is usually listed as principal author:

A Graduate Student's Guide to Determining Authorship Credit and Authorship Order, APA Science Student Council 2006

Affiliation

The primary affiliation for each author should be the institution where the majority of their work was done. If an author has subsequently moved, the current address may additionally be stated. Addresses will not be updated or changed after publication of the article.

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Adding and/or deleting authors at revision stage are generally not permitted, but in some cases it may be warranted. Reasons for these changes in authorship should be explained. Approval of the change during revision is at the discretion of the Editor-in-Chief. Please note that journals may have individual policies on adding and/or deleting authors during revision stage.

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Authors are recommended to use their ORCID ID when submitting an article for consideration or acquire an ORCID ID via the submission process.

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For cases in which a co-author dies or is incapacitated during the writing, submission, or peer-review process, and the co-authors feel it is appropriate to include the author, co-authors should obtain approval from a (legal) representative which could be a direct relative.

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In the case of an authorship dispute during peer review or after acceptance and publication, the Journal will not be in a position to investigate or adjudicate. Authors will be asked to resolve the dispute themselves. If they are unable the Journal reserves the right to withdraw a manuscript from the editorial process or in case of a published paper raise the issue with the authors' institution(s) and abide by its guidelines.

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To ensure objectivity and transparency in research and to ensure that accepted principles of ethical and professional conduct have been followed, authors should include information regarding sources of funding, potential conflicts of interest (financial or non-financial), informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals.

Authors should include the following statements (if applicable) in a separate section entitled "Compliance with Ethical Standards" when submitting a paper:

Disclosure of potential conflicts of interest

Research involving Human Participants and/or Animals

Informed consent

Please note that standards could vary slightly per journal dependent on their peer review policies (i.e. single or double blind peer review) as well as per journal subject discipline. Before submitting your article check the instructions following this section carefully.

The corresponding author should be prepared to collect documentation of compliance with ethical standards and send if requested during peer review or after publication.

The Editors reserve the right to reject manuscripts that do not comply with the above-mentioned guidelines. The author will be held responsible for false statements or failure to fulfill the above-mentioned guidelines.

Disclosure of potential conflicts of interest

Authors must disclose all relationships or interests that could have direct or potential influence or impart bias on the work. Although an author may not feel there is any conflict, disclosure of relationships and interests provides a more complete and transparent process, leading to an accurate and objective assessment of the work. Awareness of a real or perceived conflicts of interest is a perspective to which the readers are entitled. This is not meant to imply that a financial relationship with an organization that sponsored the research or compensation received for consultancy work is inappropriate. Examples of potential conflicts of interests that are directly or indirectly related to the research may include but are not limited to the following:

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Financial support for educational programs

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Financial relationships, for example equity ownership or investment interest

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In addition, interests that go beyond financial interests and compensation (non-financial interests) that may be important to readers should be disclosed. These may include but are not limited to personal relationships or competing interests directly or indirectly tied to this research, or professional interests or personal beliefs that may influence your research.

The corresponding author collects the conflict of interest disclosure forms from all authors. In author collaborations where formal agreements for representation allow it, it is sufficient for the corresponding author to sign the disclosure form on behalf of all authors. Examples of forms can be found here:

The corresponding author will include a summary statement in the text of the manuscript in a separate section before the reference list, that reflects what is recorded in the potential conflict of interest disclosure form(s).

Please make sure to submit all Conflict of Interest disclosure forms together with the manuscript.

See below examples of disclosures:

Funding: This study was funded by X (grant number X).

Conflict of Interest: Author A has received research grants from Company A. Author B has received a speaker honorarium from Company X and owns stock in Company Y. Author C is a member of committee Z.

If no conflict exists, the authors should state:

Conflict of Interest: The authors declare that they have no conflict of interest.

Research involving human participants, their data or biological material

Ethics approval

When reporting a study that involved human participants, their data or biological material, authors should include a statement that confirms that the study was approved (or granted exemption) by the appropriate institutional and/or national research ethics committee (including the name of the ethics committee) and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. If doubt exists whether the research was conducted in accordance with the 1964 Helsinki Declaration or comparable standards, the authors must explain the reasons for their approach, and demonstrate that an independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study. If a study was granted exemption from requiring ethics approval, this should also be detailed in the manuscript (including the reasons for the exemption).

Retrospective ethics approval

If a study has not been granted ethics committee approval prior to commencing, retrospective ethics approval usually cannot be obtained and it may not be possible to consider the manuscript for peer review. The decision on whether to proceed to peer review in such cases is at the Editor's discretion.

Ethics approval for retrospective studies

Although retrospective studies are conducted on already available data or biological material (for which formal consent may not be needed or is difficult to obtain) ethics approval may be required dependent on the law and the national ethical guidelines of a country. Authors should check with their institution to make sure they are complying with the specific requirements of their country.

Ethics approval for case studies

Case reports require ethics approval. Most institutions will have specific policies on this subject. Authors should check with their institution to make sure they are complying with the specific requirements of their institution and seek ethics approval where needed. Authors should be aware to secure informed consent from the individual (or parent or guardian if the participant is a minor or incapable) See also section on Informed Consent.

Cell lines

If human cells are used, authors must declare in the manuscript: what cell lines were used by describing the source of the cell line, including when and from where it was obtained, whether the cell line has recently been authenticated and by what method. If cells were bought from a life science company the following need to be given in the manuscript: name of company (that provided the cells), cell type, number of cell line, and batch of cells.

It is recommended that authors check the NCBI database for misidentification and contamination of human cell lines. This step will alert authors to possible problems with the cell line and may save considerable time and effort.

Further information is available from the International Cell Line Authentication Committee (ICLAC).

Authors should include a statement that confirms that an institutional or independent ethics committee (including the name of the ethics committee) approved the study and that informed consent was obtained from the donor or next of kin.

Research Resource Identifiers (RRID)

Research Resource Identifiers (RRID) are persistent unique identifiers (effectively similar to a DOI) for research resources. This journal encourages authors to adopt RRIDs when reporting key biological resources (antibodies, cell lines, model organisms and tools) in their manuscripts.

Examples:

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Antibody: Luciferase antibody DSHB Cat# LUC-3, RRID:AB_2722109

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RRIDs are provided by the Resource Identification Portal. Many commonly used research resources already have designated RRIDs. The portal also provides authors links so that they can quickly register a new resource and obtain an RRID.

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The World Health Organization (WHO) definition of a clinical trial is "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes". The WHO defines health interventions as “A health intervention is an act performed for, with or on behalf of a person or population whose purpose is to assess, improve, maintain, promote or modify health, functioning or health conditions” and a health-related outcome is generally defined as a change in the health of a person or population as a result of an intervention.

To ensure the integrity of the reporting of patient-centered trials, authors must register prospective clinical trials (phase II to IV trials) in suitable publicly available repositories. For example www.clinicaltrials.gov or any of the primary registries that participate in the WHO International Clinical Trials Registry Platform.

The trial registration number (TRN) and date of registration should be included as the last line of the manuscript abstract.

For clinical trials that have not been registered prospectively, authors are encouraged to register retrospectively to ensure the complete publication of all results. The trial registration number (TRN), date of registration and the words

'retrospectively registered' should be included as the last line of the manuscript abstract.

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Springer Nature advocates complete and transparent reporting of biomedical and biological research and research with biological applications. Authors are recommended to adhere to the minimum reporting guidelines hosted by the EQUATOR Network when preparing their manuscript.

Exact requirements may vary depending on the journal; please refer to the journal's Instructions for Authors.

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Observational studies (STROBE)

Systematic reviews and meta-analyses (PRISMA) and protocols (Prisma-P)

Diagnostic/prognostic studies (STARD) and (TRIPOD)

Case reports (CARE)

Clinical practice guidelines (AGREE) and (RIGHT)

Qualitative research (SRQR) and (COREQ)

Animal pre-clinical studies (ARRIVE)

Quality improvement studies (SQUIRE)

Economic evaluations (CHEERS)

Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Ethics approval'.

Examples of statements to be used when ethics approval has been obtained:

· All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or

comparable ethical standards. The study was approved by the Bioethics Committee of the Medical University of A (No. ...).

· This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University B (Date.../No. ...).

· Approval was obtained from the ethics committee of University C. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

· The questionnaire and methodology for this study was approved by the Human Research Ethics committee of the University of D (Ethics approval number: ...).

Examples of statements to be used for a retrospective study:

· Ethical approval was waived by the local Ethics Committee of University A in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

· This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the IRB of XYZ who determined that our study did not need ethical approval. An IRB official waiver of ethical approval was granted from the IRB of XYZ.

· This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of University B approved this study.

Examples of statements to be used when no ethical approval is required/exemption granted:

· This is an observational study. The XYZ Research Ethics Committee has confirmed that no ethical approval is required.

· The data reproduced from Article X utilized human tissue that was procured via our Biobank AB, which provides de-identified samples. This study was reviewed and deemed exempt by our XYZ Institutional Review Board. The BioBank protocols are in accordance with the ethical standards of our institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

Informed consent

All individuals have individual rights that are not to be infringed. Individual participants in studies have, for example, the right to decide what happens to the (identifiable) personal data gathered, to what they have said during a study or an interview, as well as to any photograph that was taken. This is especially true concerning images of vulnerable people (e.g. minors, patients, refugees, etc) or the use of images in sensitive contexts. In many instances authors will need to secure written consent before including images.

Identifying details (names, dates of birth, identity numbers, biometrical characteristics (such as facial features, fingerprint, writing style, voice pattern, DNA or other distinguishing characteristic) and other information) of the participants that were studied should not be published in written descriptions, photographs, and genetic profiles unless the information is essential for scholarly purposes and the participant (or parent/guardian if the participant is a minor or incapable or legal representative) gave written informed consent for publication. Complete anonymity is difficult to achieve in some cases. Detailed descriptions of individual participants, whether of their whole bodies or of body sections, may lead to disclosure of their identity. Under certain circumstances consent is not required as long as information is anonymized and the submission does not include images that may identify the person.

Informed consent for publication should be obtained if there is any doubt. For example, masking the eye region in photographs of participants is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic profiles, authors should provide assurance that alterations do not distort meaning.

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· Images such as x rays, laparoscopic images, ultrasound images, brain scans, pathology slides unless there is a concern about identifying information in which case, authors should ensure that consent is obtained.

· Reuse of images: If images are being reused from prior publications, the Publisher will assume that the prior publication obtained the relevant information regarding consent. Authors should provide the appropriate attribution for republished images.

Consent and already available data and/or biologic material

Regardless of whether material is collected from living or dead patients, they (family or guardian if the deceased has not made a pre-mortem decision) must have given prior written consent. The aspect of confidentiality as well as any wishes from the deceased should be respected.

Data protection, confidentiality and privacy

When biological material is donated for or data is generated as part of a research project authors should ensure, as part of the informed consent procedure, that the participants are made aware what kind of (personal) data will be processed, how it will be used and for what purpose. In case of data acquired via a

biobank/biorepository, it is possible they apply a broad consent which allows research participants to consent to a broad range of uses of their data and samples which is regarded by research ethics committees as specific enough to be considered "informed". However, authors should always check the specific biobank/biorepository policies or any other type of data provider policies (in case of non-bio research) to be sure that this is the case.

Consent to Participate

For all research involving human subjects, freely-given, informed consent to participate in the study must be obtained from participants (or their parent or legal guardian in the case of children under 16) and a statement to this effect should appear in the manuscript. In the case of articles describing human transplantation studies, authors must include a statement declaring that no organs/tissues were obtained from prisoners and must also name the institution(s)/clinic(s)/department(s) via which organs/tissues were obtained. For manuscripts reporting studies involving vulnerable groups where there is the potential for coercion or where consent may not have been fully informed, extra care will be taken by the editor and may be referred to the Springer Nature Research Integrity Group.

Consent to Publish

Individuals may consent to participate in a study, but object to having their data published in a journal article. Authors should make sure to also seek consent from individuals to publish their data prior to submitting their paper to a journal. This is in particular applicable to case studies. A consent to publish form can be found

here. (Download docx, 36 kB)

Summary of requirements

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Consent to participate' and/or 'Consent to publish'. Other declarations include Funding, Competing interests, Ethics approval, Consent, Data and/or Code availability and Authors' contribution statements.

Please see the various examples of wording below and revise/customize the sample statements according to your own needs.

Sample statements for "Consent to participate":

Informed consent was obtained from all individual participants included in the study.

Informed consent was obtained from legal guardians.

Written informed consent was obtained from the parents.

Verbal informed consent was obtained prior to the interview.

Sample statements for “Consent to publish”:

The authors affirm that human research participants provided informed consent for publication of the images in Figure(s) 1a, 1b and 1c.

The participant has consented to the submission of the case report to the journal.

Patients signed informed consent regarding publishing their data and photographs.

Sample statements if identifying information about participants is available in the article:

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

Images will be removed from publication if authors have not obtained informed consent or the paper may be removed and replaced with a notice explaining the reason for removal.

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DataCite

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APÊNDICE 1 – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

UFPR
UNIVERSIDADE FEDERAL DO PARANÁ

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO - TCLE

Nós, Rafaela Scariot - Professora departamento de Estomatologia, Nelson Luis Barbosa Rebellato – Coordenador do Setor de Ciências da Saúde e Giselle Emilãine da Silva Reis – aluna de doutorado em Clínica Odontológica – da Universidade Federal do Paraná (UFPR), estamos convidando você, mulher que irá extrair seus terceiros molares no Serviço de Cirurgia e Traumatologia Bucomaxilofaciais da UFPR a participar de um estudo intitulado "**EFEITO DAS DIFERENTES FASES DO CICLO MENSTRUAL SOBRE A PERCEPÇÃO DE DESCONFORTO CIRÚRGICO NA REMOÇÃO DE TERCEIROS MOLARES**". Essa pesquisa irá verificar se o período do seu ciclo menstrual pode influenciar na sua percepção sobre a cirurgia para extração do dente do siso. Trata-se de uma pesquisa importante devido a necessidade de identificação de fatores que influenciam no desconforto cirúrgico, visando sempre melhorar a qualidade do atendimento dos pacientes, minimizando o sofrimento.

a)O objetivo desta pesquisa é investigar o efeito das diferentes fases do ciclo menstrual, além de avaliar se características emocionais (ansiedade), características individuais (idade, peso), presença de doenças crônicas e características genéticas que influenciam na intensidade de percepção de desconforto cirúrgico durante a remoção de terceiros molares.

b)Caso você concorde em participar da pesquisa, será necessário passar por uma avaliação inicial, com coletas de dados pessoais e exame clínico para verificar existência de dor crônica na face, além de responder a dois questionários para avaliação do seu nível de ansiedade antes do procedimento a ser realizado. Logo após, também será realizada a coleta de saliva através de bochecho e raspagem de células bucais da bochecha, para avaliar marcadores genéticos relacionados a ansiedade, além disso será realizada coleta do seu sangue para avaliação dos níveis hormonais de estradiol, FSH e progesterona. Após passar pelo procedimento cirúrgico, será necessário responder um último questionário sobre a sua percepção acerca do procedimento de extração do dente do siso.

c)Para tanto você deverá comparecer nas dependências das clínicas Odontológicas da UFPR - serviço de Cirurgia e Traumatologia Bucomaxilofaciais, localizado na Avenida Pref. Lothário Meissner, CEP 80210-70, Jardim Botânico – Curitiba/PR para consultas odontológicas e preenchimento de questionário que conterá as informações necessárias para este estudo, o que levará cerca de 10 minutos para cada etapa da pesquisa.

d)É possível que você experimente algum desconforto, principalmente relacionado ao cansaço devido às várias etapas da pesquisa, desconforto durante raspagem da mucosa jugal e incômodo durante a coleta de sangue.

e)Alguns riscos relacionados ao estudo podem ser: constrangimentos durante a coleta de dados, alguma dor ou desconforto durante a coleta de sangue, leve desconforto na raspagem de células bucais da bochecha após a coleta de saliva. Devido a esse fato, as entrevistas se darão em um ambiente adequado e particular, e em caso de desconforto será opção do

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Alto da Glória | Curitiba/PR | CEP 80060-240 | cometica.saude@ufpr.br – telefone (041) 3360-7259

paciente continuar ou não com a pesquisa, sendo as informações restritas somente aos pesquisadores em questão.

f)Os benefícios esperados com essa pesquisa são uma melhor compreensão dos fatores que contribuem para as diferenças individuais na dor, inclusive conhecimento do melhor período do ciclo menstrual para agendamento de cirurgias eletivas para remoção de terceiros molares, o que pode levar ao desenvolvimento melhores protocolos de atendimento, que reduzam o sofrimento dos pacientes em procedimentos cirúrgicos para remoção dentária.

g)Os pesquisadores Rafaela Scariot, Giselle Emiläine da Silva Reis, Nelson Luis Barbosa Rebellato, responsáveis por este estudo poderão ser localizados no bloco do Curso de Odontologia da UFPR localizado na Avenida Pref. Lothário Meissner, CEP 80210-70, Jardim Botânico – Curitiba/PR ou através do telefone (41) 3360-4053, nas terças e quintas-feiras das 13h30min às 17h, na sala da Pós-graduação em Cirurgia Buco-maxilo-facial, ou através dos e-mails rafaela_scariot@yahoo.com.br, gisellereis_86@hotmail.com, rebelato@ufpr.br, para esclarecer eventuais dúvidas que você possa ter e fornecer-lhe as informações que queira, antes, durante ou depois de encerrado o estudo. Em caso de emergência o você também pode me contatar neste número, em qualquer horário : 3360-4053.

h)A sua participação neste estudo é voluntária e se você não quiser mais fazer parte da pesquisa poderá desistir a qualquer momento e solicitar que lhe devolvam este Termo de Consentimento Livre e Esclarecido assinado. O seu atendimento está garantido e não será interrompido caso o você desista de participar.

i)O material obtido – amostras biológicas, questionários, imagens e vídeos – será utilizado unicamente para essa pesquisa e será destruído/descartado (informar o destino que será dado ao material) ao término do estudo, dentro de 2,5 anos.

j)As informações relacionadas ao estudo poderão ser conhecidas por pessoas autorizadas. – orientador, pesquisadores colaboradores da pesquisa, sob forma codificada, para que a sua **identidade seja preservada e mantida sua confidencialidade, a menos que seja seu desejo ter identidade revelada.**

k)As despesas necessárias para a realização da pesquisa (análise genética e hormonal) não são de sua responsabilidade e você não receberá qualquer valor em dinheiro pela sua participação. Entretanto, caso seja necessário seu deslocamento até o local do estudo os pesquisadores asseguram o ressarcimento dos seus gastos com transporte (Item II.21, e item IV.3, sub-item g, Resol. 466/2012).

l)Quando os resultados forem publicados, não aparecerá seu nome, e sim um código.

Participante da Pesquisa e/ou Responsável Legal: _____
Pesquisador Responsável ou quem aplicou o TCLE :_____
Orientador: _____

Comitê de Ética em Pesquisa com Seres Humanos do Setor de Ciências da Saúde da UFPR | CEP/SD Rua Padre Camargo, 285 | 1º andar |
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m)Se você tiver dúvidas sobre seus direitos como participante de pesquisa, você pode contatar também o Comitê de Ética em Pesquisa em Seres Humanos (CEP/SD) do Setor de Ciências da Saúde da Universidade Federal do Paraná, pelo e-mail cometica.saude@ufpr.br e/ou telefone 41 -3360-7259, das 08:30h às 11:00h e das 14:00h.às 16:00h. O Comitê de Ética em Pesquisa é um órgão colegiado multi e transdisciplinar, independente, que existe nas instituições que realizam pesquisa envolvendo seres humanos no Brasil e foi criado com o objetivo de proteger os participantes de pesquisa, em sua integridade e dignidade, e assegurar que as pesquisas sejam desenvolvidas dentro de padrões éticos (Resolução nº 466/12 Conselho Nacional de Saúde).

Eu,_____ li esse Termo de Consentimento e compreendi a natureza e o objetivo do estudo do qual concordei em participar. A explicação que recebi menciona os riscos e benefícios. Eu entendi que sou livre para interromper minha participação a qualquer momento sem justificar minha decisão e sem qualquer prejuízo para mim e sem que esta decisão afete meu tratamento.

Eu concordo, voluntariamente, em participar deste estudo.

Curitiba, ___ de _____ de 20___

_____

[Assinatura do Participante de Pesquisa ou Responsável Legal]

Eu declaro ter apresentado o estudo, explicado seus objetivos, natureza, riscos e benefícios e ter respondido da melhor forma possível às questões formuladas.

_____

[Assinatura do Pesquisador Responsável ou quem aplicou o TCLE]

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APÊNDICE 2 – FICHA CLÍNICA

UNIVERSIDADE FEDERAL DO PARANÁ

SETOR DE CIÊNCIAS DA SAÚDE

DEPARTAMENTO DE ESTOMATOLOGIA

Número:

FICHA DE AVALIAÇÃO INDIVIDUAL

Data da Avaliação: _____/_____/_____ Hora de início: _____Hora de Término: _____

IDENTIFICAÇÃO DO PACIENTE

Iniciais: _____ Raça: _____

Idade: _____ Data de Nascimento: _____/_____/_____

Peso: _____ Altura:_____ IMC:_____

Você já extraiu algum dente antes? ( ) SIM ( ) NÃO

Você tem alguma experiência de extração dentária anterior, que tenha sido traumática? ( ) SIM ( ) NÃO

De 0 a 10, o quanto doeu durante a coleta de sangue? _____

Você possui algum tipo de dor crônica no corpo ou no rosto? ( ) SIM ( ) NÃO

Você toma algum medicamento? ( ) SIM ( ) NÃO

INFORMAÇÕES SOBRE O CICLO MENSTRUAL

Data de início última menstruação: _____/_____/_____ Data de término última menstruação: _____/_____/_____

Uso de contraceptivo oral:	( ) Sim ( ) Não
Uso de contraceptivo injetável:	( ) Sim ( ) Não
Uso de adesivo transdérmico:	( ) Sim ( ) Não
Uso de dispositivo intrauterino de levonogerstrel:	( ) Sim ( ) Não
Terapia para reposição hormonal:	( ) Sim ( ) Não
Número de gestações	( ) 1 ( ) 2 ou +
Tem filhos	( ) Sim ( ) Não

DADOS CIRÚRGICOS – DENTES EXTRAÍDOS

( ) 18 ( ) 28 ( )38 ( )48

SITUAÇÃO DO DENTE EXTRAÍDO

18	( ) hígido	( ) cariado	( ) fraturado	( ) raiz residual
28	( ) hígido	( ) cariado	( ) fraturado	( ) raiz residual
38	( ) hígido	( ) cariado I	( ) fraturado	( ) raiz residual
48	( ) hígido	( ) cariado	( ) fraturado	( ) raiz residual

NÚMERO DE RAÍZES DO DENTE EXTRAÍDO

18	( ) 1	( ) 2	( ) 3	( ) 4
28	( ) 1	( ) 2	( ) 3	( ) 4
38	( ) 1	( ) 2	( ) 3	( ) 4
48	( ) 1	( ) 2	( ) 3	( ) 4

	CURVATURA RADICULAR			GRAU DIVERGÊNCIA RADICULAR		
18	( ) Não possui	( ) Pequena	( ) Acentuada	( ) Não possui	( ) Pequeno	( ) Acentuado
28	( ) Não possui	( ) Pequena	( ) Acentuada	( ) Não possui	( ) Pequeno	( ) Acentuado
38	( ) Não possui	( ) Pequena	( ) Acentuada	( ) Não possui	( ) Pequeno	( ) Acentuado
48	( ) Não possui	( ) Pequena	( ) Acentuada	( ) Não possui	( ) Pequeno	( ) Acentuado

PROPORÇÃO COROA/RAIZ

18	( ) Comprimento da coroa é maior do que o da raiz	( ) Comprimento da coroa é igual ao da raiz	( ) Comprimento da coroa é menor do que o da raiz
28	( ) Comprimento da coroa é maior do que o da raiz	( ) Comprimento da coroa é igual ao da raiz	( ) Comprimento da coroa é menor do que o da raiz
38	( ) Comprimento da coroa é maior do que o da raiz	( ) Comprimento da coroa é igual ao da raiz	( ) Comprimento da coroa é menor do que o da raiz
48	( ) Comprimento da coroa é maior do que o da raiz	( ) Comprimento da coroa é igual ao da raiz	( ) Comprimento da coroa é menor do que o da raiz

PRESENÇA DE REABSORÇÃO INTERNA/ESTERNA RADICULAR

18 ( ) Sim ( ) Não

28 ( ) Sim ( ) Não

38 ( ) Sim ( ) Não

48 ( ) Sim ( ) Não

FOI NECESSÁRIO REALIZAR

18 ( ) Osteotomia ( ) Odontosecção ( ) Não

28 ( ) Osteotomia ( ) Odontosecção ( ) Não

38 ( ) Osteotomia ( ) Odontosecção ( ) Não

48 ( ) Osteotomia ( ) Odontosecção ( ) Não

CLASSIFICAÇÃO RADIOGRAFICA DE WINTER

18 ( ) mesioangular ( ) Horizontal ( ) Vertical ( ) Distoangular

28 ( ) mesioangular ( ) Horizontal ( ) Vertical ( ) Distoangular

38 ( ) mesioangular ( ) Horizontal ( ) Vertical ( ) Distoangular

48 ( ) mesioangular ( ) Horizontal ( ) Vertical ( ) Distoangular